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Contents on Inside Cover

American Heart Journal

CONTENTS FOR DECEMBER, 1947

Original Communications

Clinical Reports

Abstracts and Reviews

Index

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American Heart Journal

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Original Communications

NORMAL VARIATIONS IN MULTIPLE PRECORDIAL LEADS

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ALTHOUGH precordial leads have been used clinically for fifteen years, there is still no general agreement as to the minimal number of leads necessary for an adequate examination. The advisability of multiple precordial leads was early emphasized by Wilson and associates as a result of their experience with direct leads in animals[1-3] and in the exposed human heart,[4] and has been supported by a vast amount of clinical data, not only from the Wilson group[5] but also from many other sources. Nevertheless, there is lack of extensive studies correlating findings in multiple precordial leads with those at necropsy. This may in part account for the fact that many cardiologists, perhaps the majority, are still content with a single precordial lead.

To fulfill an apparent need, a comprehensive study correlating electrocardiographic and autopsy findings was commenced in 1941 and is still in progress. To date 1,000 cases in which multiple precordial leads were taken during life have been followed to necropsy.* In 439 of these, post-mortem examination included injection of the coronary arteries with radiopaque mass, roentgenogram, and subsequent dissection with multiple microscopic blocks. The data obtained through the electrocardiographic-autopsy correlations will form the basis for a series of papers.

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*We are greatly indebted to Dr. S. E. Gould, Pathologist at Wayne County General Hospital, for permission to make free use of his autopsy files on cases we previously had studied electrocardiographically.

GENERAL PROCEDURE

Electrocardiographic Study.—The central terminal of Wilson and co-workers[6] has been employed throughout this study in order to minimize the influence of the indifferent electrode, and thereby obtain as accurate a record as possible of the potential variations of the exploring electrode. When the remote electrode is connected to all three extremities through the central terminal, its potential variations are reduced to an almost negligible quantity which at the most does not exceed 0.3 millivolt.[7-9] On the other hand, when the remote electrode is applied to a single extremity its potential variations are subject to a much wider range, depending upon cardiac position and other factors, and are often large enough to distort the recordings from the precordial electrode, as shown by the significant differences in the pattern obtained by CR, CL, and CF leads.[10] More recently, Wolferth and associates[11] have criticized the central terminal and have advocated application of the remote electrode to the spine of the right scapula. However, the potential variations in this region usually correspond to those of the right arm and precordial leads obtained with the remote electrode on the spine of the scapula closely resemble the CR leads.[12] Thus, the central terminal appears preferable to any arrangement in which the remote electrode is applied to a single point.

At the beginning of this project the routine electrocardiogram in this laboratory included merely the standard limb leads and precordial Leads V_2, V_4, and V_6. As the study progressed it became evident that leads from all six standard precordial reference points were advisable as a routine and that additional leads to the right, to the left, or above the customary positions were indicated under special circumstances. Furthermore, it was found that the augmented unipolar limb leads of Goldberger[13] yielded valuable information regarding the portion of the heart resting on the diaphragm[14] and that facing each arm, and have aided considerably in the analysis of the standard extremity leads. As a consequence, all electrocardiograms taken in this laboratory since 1943 have comprised Leads I, II, III, aV_R, aV_L, aV_F, V_1, V_2, V_3, V_4, V_5, and V_6. More recently Lead V_{3R} has been added to the routine, because of the information yielded in the diagnosis of right ventricular lesions.[15]

All tracings have been taken with the Cambridge mobile unit. To expedite the task of the technician, the electrocardiograph has been equipped with a multiple lead switch* constructed on the principle described by Ethridge and Stolar.[16] The switch has an outlet wire for each of the three extremities and a fourth outlet wire permanently connected to the precordial electrode. The standard and Goldberger limb leads and Wilson precordial leads may be taken successively merely by moving the dial of the multiple lead switch without disturbing the connections to the patient. The switch is constructed so that the Wilson lead and each of the Goldberger leads may be taken with or without the inclusion of a 5000 ohm resistance in every connection of the indifferent electrode. The resistance is always advisable to minimize current flowing through the skin.[17]

*The multiple lead switch used in this laboratory was constructed by Mr. L. A. Boulet, Detroit, Mich.

Method of Pathologic Study.—The heart was removed by transection of the great vessels at their exit from the pericardium. The radiopaque mass used for injection of the coronary circulation consisted of a lead acetate-agar mixture.[18] At the outset of the study, differently colored mixtures were injected simultaneously into the right and left coronary arteries under controlled pressures according to the technique of Schlesinger.[18] This method of injection was time consuming and, in our experience, often failed to fill portions of the coronary tree which subsequently proved to be patent. Since our chief interest lay in the accurate localization of myocardial rather than coronary lesions, the roentgenogram of the injected heart was employed more as a map on which the position of lesions detected by gross or microscopic examination could be plotted. For our purposes, it was desirable to outline all grossly visible ramifications of the coronary tree that were not occluded by an adherent thrombus or placque.

In order to simplify the procedure to a point where it could be used routinely, the injection technique was modified as follows: The cannulated left and right coronary arteries were injected successively with a warm uncolored lead agar mass from a hand syringe, using a pulsatile movement of the plunger. The injection was continued until the vessel was visibly distended or a resistance was encountered, whereupon the cannula was removed and a ligature tightened.

Injection from a syringe generally filled all grossly visible branches of the coronary arteries except the first branch of the right coronary which supplies a portion of the anterior aspect of the right ventricle. It was usually necessary to insert the cannula beyond the orifice of this branch in order to secure it firmly in place. Occasional failures to fill other patent branches, especially the posterior descending coronary artery, were encountered, but were much less common than with the Schlesinger technique of injection. It must be realized that injection from a syringe may dislodge ante-mortem thrombi that were not firmly adherent to the walls of a coronary artery and, therefore, may render visible portions of the coronary tree that were obstructed prior to death. It is also evident that the hearts injected by the syringe technique were not suitable for a reconstruction of the distribution of the right and left coronary circulation during life or for an evaluation of the direction of flow in anastomotic channels. These limitations of the syringe technique did not detract from the chief objective of this study, which was to correlate electrocardiographic findings with gross and histologic changes in the myocardium.

The heart was refrigerated overnight to harden the injection mass before sectioning. A modified Klotz solution[19] was used as a preservative, in order to minimize color change and shrinkage. The Schlesinger method of sectioning,[18] used in our first 167 cases, allows an unrolling of the cone-shaped heart so that both ventricles and the entire coronary tree are laid out flat for roentgenography. Although this is well adapted for the study of the coronary tree, it has two serious drawbacks from the standpoint of fulfilling our purposes, namely: (1) the roentgenogram gave no help in locating the position of lesions with reference to the endocardial or epicardial surface, since the entire thickness of myocardium was superimposed on the film; (2) the roentgenogram gave no help in

tracing the continuity of lesions from the anterior or posterior walls into the septum, since the latter was removed in the process of sectioning.

To overcome the disadvantages of the Schlesinger technique of opening the heart, a method of sectioning into transverse slices was substituted. The ventricles were first separated from the atria at the valvular ring by a transverse section parallel with the atrioventricular groove. The ventricles were then cut into a series of transverse slices 1 cm. thick.[20] These slices were placed on a cassette so that in the finished roentgenogram the apical segment was located in the upper left hand corner and intervening segments were arranged in rows from left to right and from above downward, ending with the most basal segment in the lower right hand corner. Each slice was placed so that the anterior surface of the ventricles was uppermost and the lateral walls of the left and right ventricles faced the left and right edges of the film, respectively. This method was used for the last 272 cases and proved more suitable for our purposes than the Schlesinger method of opening the heart.

The electrocardiographic diagnosis was made prior to the examination of any autopsy material. A careful gross examination of each transverse slice was made in conjunction with the roentgenogram of the injected heart and with knowledge of the electrocardiographic findings. The exact location of gross lesions was drawn on the roentgenogram with a wax pencil. When the lesions were too patchy or irregular to depict in this manner, color photographs were taken for future reference. The extent of small lesions was further investigated by additional transverse slices in the original segment. All evident and suspicious gross lesions were checked by microscopic blocks, which were taken so as to include the entire thickness of the ventricular wall. In the absence of gross lesions, the number and location of microscopic blocks depended upon the clinical and electrocardiographic findings. When a lesion was suspected from the electrocardiogram, the injection studies, or the gross appearance, but could not be positively identified or delineated by gross examination, it was customary to take a series of blocks around the entire circumference of the ventricle at one or more levels. The location of all microscopic sections was marked on the roentgenogram with wax pencil. Sections were read at a later date without knowledge of clinical or gross findings. Whenever there was a discrepancy between the electrocardiographic, gross, and microscopic findings, the gross specimen was re-examined and additional sections taken. If the microscopic sections failed to confirm the gross diagnosis, the outlines of the lesion as drawn on the roentgenogram were corrected so as to correspond with the microscopic findings. All major coronary arteries were opened by multiple transverse sections to check roentgenographic findings as to patency or obstruction, and to estimate degree of sclerosis. The relative size of the right and left ventricles was estimated in two different ways: (1) Measurements of the thickness of the roentgen image of the right and left ventricular walls were made at a number of points and the range and average thickness of each ventricle determined. (2) The ventricular segments were separated through an incision made at their juncture in the interventricular septum according to the technique of Stofer and Hiratzka,[20] and a

ratio was calculated, using the combined weights of the left ventricular segments as the numerator and the combined weights of the right ventricular segments as the denominator.

Material.—In this communication, an analysis is presented of the precordial electrocardiograms of the cases whose hearts were considered normal at autopsy on the basis of the following criteria: total weight below 400 grams in the male and below 350 grams in the female; ventricular ratio in the normal range of 1.6 to 2.0; normal myocardium to gross and microscopic examination.

A total of fifty-two cases satisfied the foregoing criteria and forms the basis of this study. The youngest patient was 19 years of age and the eldest was 87. The distribution by decade was as follows: second, one case; third, four cases; fourth, eight; fifth, eight; sixth, thirteen; seventh, fourteen; eighth, three; and ninth, one case. The series comprised thirty-six men and sixteen women. Death was due to noncardiac causes in all cases, the major factors being malignancy in nineteen, cirrhosis in nine, terminal pneumonia in seven, tuberculosis in four, postoperative in four, and miscellaneous conditions in the remainder. The precordial electrocardiogram consisted of Leads V_1 through V_6 inclusive in twenty-five cases and of Leads V_2, V_4, and V_6 in the remainder.

By means of a Cambridge measuring device,* the following intervals were determined in Leads V_1, V_2, V_5, V_6, aV_R, and aV_L: time from onset of QRS to (1) nadir of Q, (2) peak of R, (3) nadir of S, and (4) end of QRS. At least three representative complexes were measured in each lead and the average value was taken. Electrocardiograms were discarded as unsuitable for measurement when the response to the standardizing current consumed more than 0.02 second or when overshooting was present. Although the measurements were made to the nearest thousandth of a second, the error reached ± 0.005 second in some cases due to difficulty in determination of the precise onset or end of the QRS. Measurements by the Cambridge device are too time consuming for general usage and estimations with the aid of a hand lens are sufficiently accurate for routine electrocardiographic interpretation.

The average amplitude of each phase of the QRS was also determined, measurements being made from the top of the isoelectric line to the peak of an upright deflection and from the bottom of the isoelectric line to the nadir of a downward deflection. Correction was made for errors of standardization. The position of the RS-T junction in reference to the isoelectric line, the contour of the RST segment, and the direction and amplitude of the T wave were also recorded.

RESULTS

P wave was invariably upright in Leads V_4, V_5, and V_6. It was usually less than 1.0 mm. in amplitude and did not exceed 2.0 millimeters. In Leads V_1, V_2, and V_3 an upright P wave was the most frequent finding, but a diphasic ($\pm$) deflection was present in V_1 in 32 per cent, in V_2 in 10 per cent, and in V_3 in 8

*We are greatly indebted to Dr. Frank N. Wilson for the loan of his Cambridge measuring instrument and for much helpful advice and criticism.

per cent of the cases. The diphasic P waves showed a steep intrinsicoid deflection, indicating proximity of the electrode to the right atrium. The amplitude of these diphasic P waves, measured from the isoelectric line to the peak of the positive or to the nadir of the negative phase, did not exceed 2 millimeters. An inverted P wave was encountered in V_1 in only one case.

Duration of QRS was determined in Leads V_2 and V_6 in all fifty-two cases and in Leads V_1 and V_5 in twenty-five of the group. The results are recorded in Table I. The measurement in Lead V_2 was, as a rule, slightly greater than in leads further removed from the heart, such as V_6. Such a discrepancy would suggest that a portion of the tracing at the beginning or end of the QRS was isoelectric in the more remote precordial leads, due to decrement of potential with increasing distance from the heart. The QRS interval in Lead V_2 ranged from 0.064 second to 0.098 second, and averaged 0.078 second. It is noteworthy that the longest QRS interval in this series did not exceed 0.10 second in any of the leads measured. When QRS duration was compared with heart weight, a trend was found toward slightly longer QRS duration with increasing weight, but no close correlation could be made out. The longest QRS interval in any precordial lead averaged 0.077 second in the cases whose heart weight was below 250 grams, 0.079 second in those with cardiac weight between 250 and 300 grams, and 0.081 second in those in the 300 to 350 gram range.

Time of Onset of Intrinsicoid Deflection.—The time interval from the onset of the QRS to the peak of the R wave (that is, onset of intrinsicoid deflection) is a rough measure of the time elapsing from the arrival of the impulse in the ventricles to the completion of activation of the segment of wall beneath the exploring electrode. This interval was invariably shortest in Lead V_1, progressively increased as the electrode was moved toward the left, and was longest in Lead V_6 in all but three cases, where it was maximal in V_5. In these cases the voltage and total duration of the QRS was greater in Lead V_5 than in V_6, suggesting that the string may have been isoelectric in Lead V_6 for a brief period at the beginning of ventricular activation. The difference in time of onset of the intrinsicoid deflection in leads over the right and left ventricles is significant, as shown by measurements ranging up to 0.023 second and averaging 0.014 second in Lead V_1, and measurements ranging from 0.020 to 0.050 second and averaging 0.034 second in Lead V_6. The measurements in a representative lead over the left ventricle exceeded those in a representative lead over the right ventricle by 0.03 second in one case, 0.025 to 0.03 second in five cases, 0.02 to 0.025 second in fourteen cases, 0.015 to 0.02 second in fifteen cases, 0.010 to 0.015 second in three cases, and by less than 0.010 second in two cases. Figures were not derived for eleven cases due to insufficient leads over the right ventricle. The maximal time interval from onset of QRS to peak of R could not be correlated with heart weight in the group of normal hearts, as shown by an average value of 0.035 second for those with heart weight below 250 grams, 0.033 second for those between 250 and 300 grams, and 0.036 second for the cases in the 300 to 350 gram range.

TABLE I. FINDINGS IN CHEST LEADS OF FIFTY-TWO PERSONS WHOSE HEARTS WERE NORMAL

LEAD	TOTAL NO. CASES	NO. WITH QS	NO. WITH Q	AMPLITUDE															DURATION													
				Q WAVE			R WAVE				S WAVE				$\frac{R}{S}$ RATIO			TOTAL QRS			ONSET QRS TO NADIR OF Q			ONSET QRS TO PEAK OF R			ONSET R TO PEAK OF R			ONSET OF QRS TO NADIR OF S		
				MIN.	MAX.	AV.	NO.	MIN.	MAX.	AV.	NO.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.
V_1	25	4	0	0	0	0	21	0	7	2.3	25	2.	24	10.5	0	0.4	4.5	.058	.092	.077	0	0	0	0	.023	.014	0	.023	.014	.017	.059	.040
V_2	52	2	0	0	0	0	50	0	12	4.7	52	5.	38	13.4	0	0.50	2.76	.064	.098	.078	0	0	0	0	.036	.018	0	.036	.018	.025	.055	.045
V_3	25	0	0	0	0	0	25	2	27	8.6	25	3.	21	8.8	7.	0.25	1.2															
V_4	52	0	4	0	2	.076	52	2	25	13.0	52	0.5	14	5.4	1.42	0.02	0.41															
V_5	25	0	10	0	1	0.24	25	3	21	10.7	17	0	10	1.7	0.75		0.16	.059	.089	.075	0	.016	.012	.014	.051	.030	.014	.037	.026	0	.075	.052
V_6	52	0	33	0	2	0.49	52	3	19	9.2	17	0	3	0.42	0.4		0.05	.062	.098	.075	0	.022	.012	.020	.050	.034	.020	.037	.027	0	.076	.053

Duration of R Wave.—The time interval from onset of the R wave to its peak is representative of the time required for the impulse to pass through the segment of ventricular wall beneath the exploring electrode. This interval was invariably shortest in Lead V_1, increased progressively in leads further to the left, and usually reached a maximum in Lead V_6, occasionally in V_5. The duration of the R wave in Lead V_1 ranged from 0 to 0.023 second, averaging 0.014 second; in Lead V_6 the range was from 0.020 to 0.037 second and the aver-

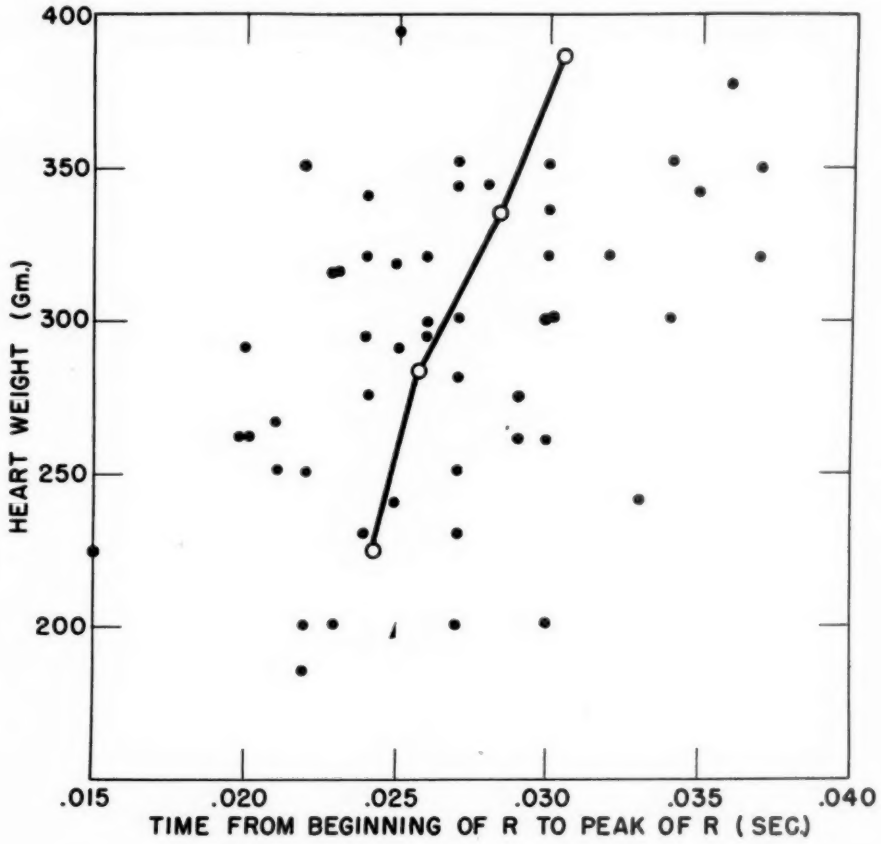

Chart I. Relation of duration of ascending limb of R wave in Leads V_5 or V_6 to heart weight.

age was 0.027 second. The measurement in a representative lead over the left ventricle exceeded that in a representative lead over the right ventricle by 0.02 to 0.025 second in four cases, 0.015 to 0.02 second in nine, 0.01 to 0.015 second in thirteen, and by less than 0.01 second in fifteen cases. When the time interval from onset to peak of R wave was plotted against heart weight, a trend was found toward a slightly longer duration of the R wave with increasing cardiac weight (Chart I). The maximal duration of the R averaged 0.024 second in the cases of patients with cardiac weight below 250 grams, 0.026 second in those between 250 and 300 grams, and 0.028 second in those in the 300 to 350 gram range.

Duration of Initial Deflection of QRS.—In Lead V_1 a small initial R, followed by a deep S, was found in twenty-one cases, and a QS deflection was the sole representative of the complex in the other four tracings. The initial deflection in Lead V_2 was upright in fifty cases. In the two remaining cases, a QS complex in V_2 accompanied a similar deflection in Lead V_1, as illustrated by Fig. 1, *B*. The initial deflection in Lead V_3 was upright in all twenty-five cases in this series. However, when V_3 exhibits a tall R wave of left ventricular origin, a very small initial Q wave may be found in this as well as in leads further to the left. The incidence of an initial Q wave was 7.7 per cent in Lead V_4, 40 per cent in V_5, and 63.4 per cent in Lead V_6. Illustrations are given in Fig. 1, *C*, *D*, *F*, and *G* and Fig. 2, *B*, *E*, and *H*. The maximal voltage of the Q wave in these three leads was 0.2 millivolt. The amplitude of the Q wave was invariably less than 25 per cent of the amplitude of the succeeding R wave. The ratio of Q to R ranged from 3 per cent to 20 per cent in Lead V_6 and from 3 per cent to 12 per cent in Lead V_5. The time interval from onset to nadir of the Q wave was short, as exemplified by the measurements in Lead V_6, which ranged from 0.006 second to 0.022 second, and averaged 0.012 second.

Location of Transitional Zone and Zones of Reference of the Potential Variations of the Right and Left Ventricles.—If a sufficient series of precordial leads is taken to cover both ventricles, a sharp contrast should be demonstrable between tracings from the left axilla (that is, Lead V_6), which reflect the potential variations of the epicardial surface of the left ventricle, and tracings from the right side of the precordium (that is, Lead V_1), which reflect principally the potential variations of the right ventricle. A study of Fig. 1 reveals that the $\frac{R}{S}$ ratio in Lead V_6 differs strikingly from that in Lead V_1 in every tracing except those of Case F, which will be discussed separately later. Furthermore, a transition from the pattern in V_1 to that in V_6 is demonstrable in leads from intervening points in all tracings of Fig. 1 except those of Case F. Among the remaining twenty-four normal cases in which all six of the precordial leads were available, the R wave first exceeded the S wave in Lead V_3 in thirteen cases (for example, Fig. 1, *C* and *I*), in V_4 in nine cases (for example, Fig. 1, *G*), and in Lead V_5 in two cases (Fig. 1, *A* and *H*).

The transition is sometimes abrupt, as in Fig. 1, *G*, where Lead V_3 displays a small R and deep S and the adjoining Lead V_4 displays a tall R and small S. Since the QRS complex in Lead V_3 resembles that in leads further to the right, and the QRS in V_4 corresponds to that in leads further to the left, it would appear that the electrode lies over the right ventricle at Position V_3 and crosses the interventricular septum to lie over the left ventricle at Position V_4. An abrupt transition between two successive precordial leads tends to occur when the septum is more or less perpendicular to the pathway of the electrode across the precordium. In other cases the transitional zone is marked by a slurred or notched complex of relatively low voltage, composed of an R and S deflection of approximately equal amplitude. Such complexes are intermediate in form between those of right and of left ventricular origin and are presumably ob-

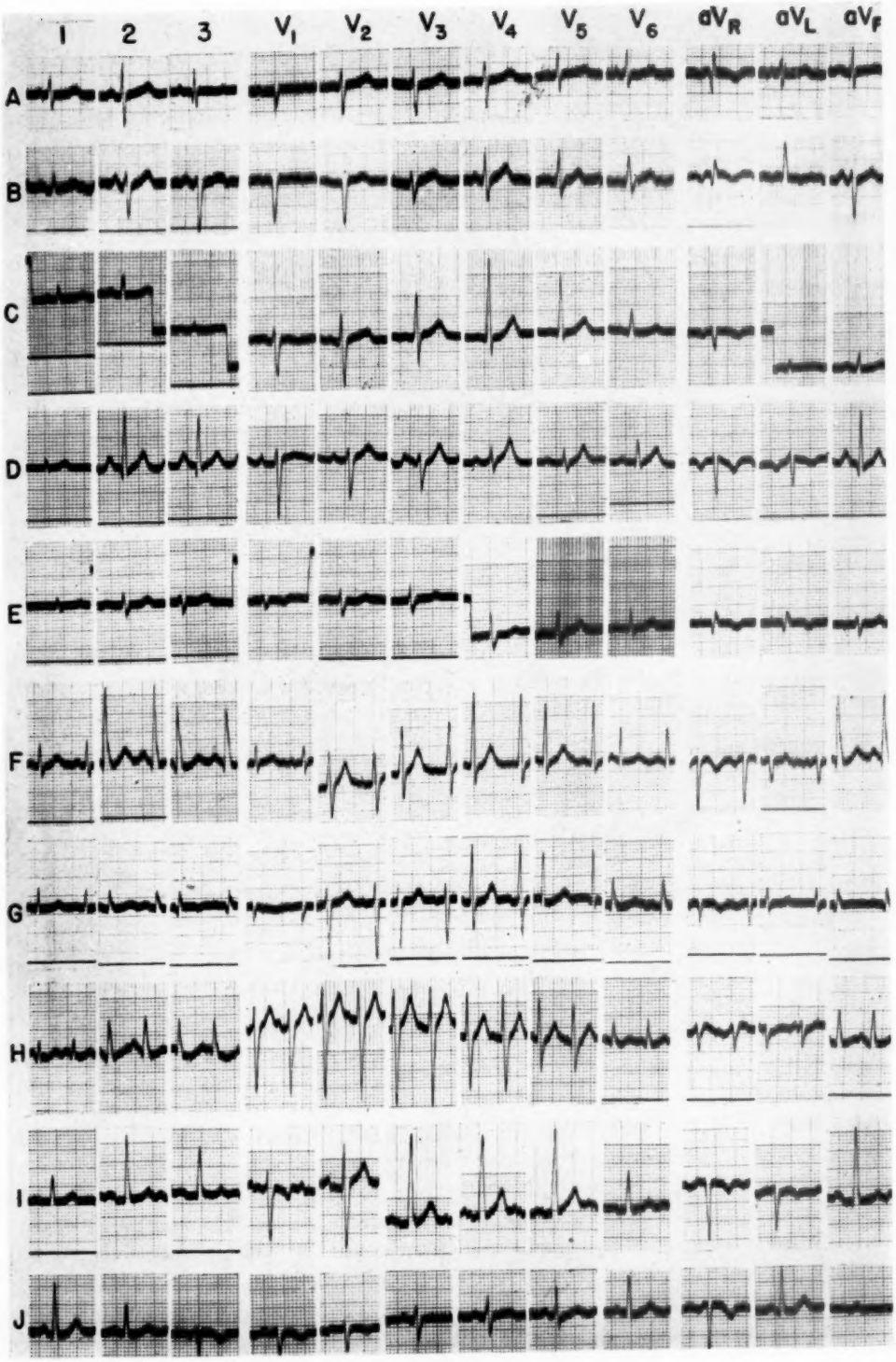

Fig. 1.—Normal variations in the precordial leads.

tained when the precordial electrode lies over the interventricular septum. A more gradual transition may occur when the apex is displaced backward, or the pathway of the electrode from Position V_2 to Position V_4 is parallel to the septum, as illustrated by Fig. 1, *A*, *D*, and *E*. The relatively low voltage and slurring of the QRS in Leads V_3, V_4, and V_5 of Fig. 1, *D* would suggest that the pathway of the electrode is nearly parallel to the septum.

Voltage of QRS.—The amplitude of both the R and S waves in every precordial lead is normally subject to wide variation, as is evident from study of Table I. The greatest range was found in Lead V_3 or V_4, depending upon whether the electrode was at the transitional zone, to the right, or to the left. Although R waves of large amplitude tend to be associated with ventricular hypertrophy, voltages in the same range were found in several normal cases in this series. Low voltage R waves less than 0.7 millivolt in all six precordial leads were found in four normal subjects in this series, as illustrated by Fig. 1, *A*, *D*, and *E*.

Relative Amplitude of the R and S Waves in Each Precordial Lead.—The voltage of the R wave was invariably less in Lead V_1 than in any other lead. The R wave was absent from Lead V_1 in four of the twenty-five cases and was relatively small in the remainder, ranging from 1 mm. to 7 mm., and averaging 2.3 millimeters. As the electrode was moved toward the left, a progressive increase in the amplitude of the R was noted in every case to reach a maximum at Position V_3 in four cases, at V_4 in thirteen cases, at V_5 in six cases, and at Position V_6 in two cases. On the other hand, the S wave attained its maximal amplitude in leads over the right ventricle, sometimes at Position V_1, as in the case shown in Fig. 1, *D*, but more often at Position V_2, as shown in Fig. 1, *G*. As the electrode was moved from positions over the right to postitions over the left ventricle, the S wave progressively diminished and was either absent from Lead V_6 or of minimal amplitude in this lead. The relationship of the R and S waves in each precordial lead is best expressed in terms of a ratio, calculated with the amplitude of R as a fixed figure in the numerator and the proportionate amplitude of S as a variable figure in the denominator. The ratio of R to S was always lowest in Lead V_1 and progressively increased as the electrode was moved to the left. This is illustrated by the average values for $\frac{R}{S}$ ratio, which were $\frac{1}{4.5}$ in Lead V_1, $\frac{1}{2.8}$ in V_2, $\frac{1}{1.2}$ in V_3, $\frac{1}{0.41}$ in V_4, $\frac{1}{0.16}$ in V_5, and $\frac{1}{0.04}$ in Lead V_6. These figures bring out the reciprocal relationships of the R and S waves in leads over the right and left ventricles.

Contour of QRS.—The QRS in the precordial leads is normally smooth in contour except when the complex is of low voltage or when the lead is at the transitional zone. Since the thickness of the string shadow is proportional to the distance traversed in a given period of time, the shadow cast by a QRS deflection of low voltage will be much thicker than that cast by a deflection of high voltage completed in the same period of time. This tends to convey the

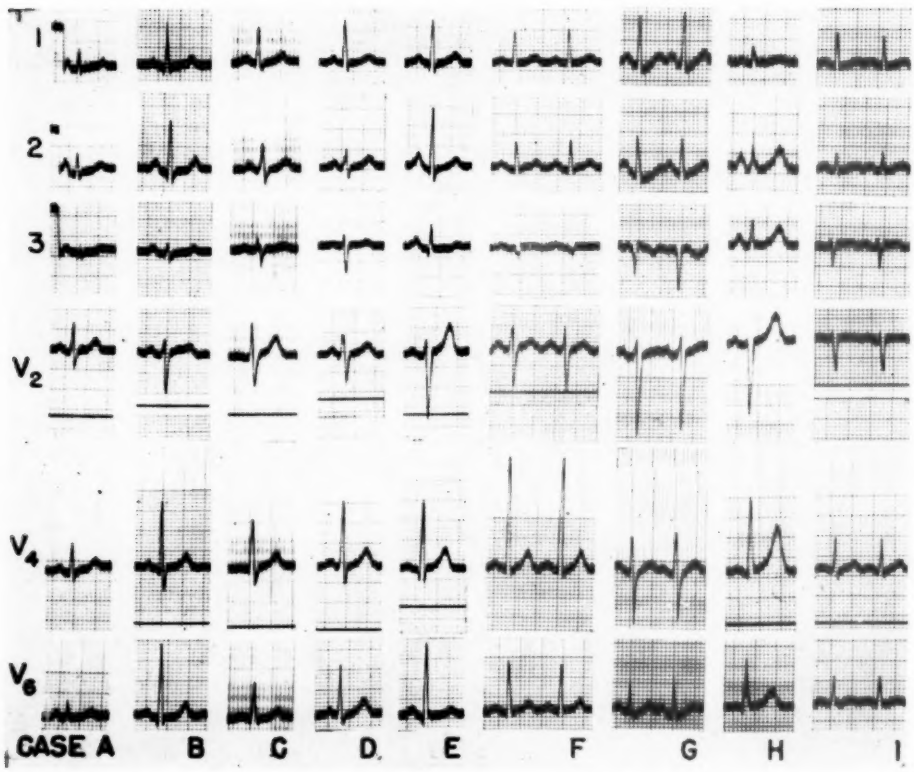

Fig. 2.—Normal variations in the precordial leads.

impression that a QRS of low voltage is slurred, as exemplified by Fig. 1, *E*. The fact that the duration of the QRS is within the normal limits of 0.10 second indicates that the relatively thick QRS tracing is secondary to the low voltage and not due to an intraventricular conduction defect. The QRS registered at the transitional zone, with the exploring electrode lying over the interventricular septum, may normally exhibit notching or slurring (as in Lead V_2 of Fig. 2, *B* and *D*, and in Leads V_3 and V_4 of Fig. 1, *D*), probably due to a greater admixture of potential variations from the two ventricles.

QT interval was below the upper limits of normal, as determined from the table of Ashman and Hull,[21] in all but two cases where borderline values were obtained.

RS-T junction was determined in portions of Leads V_1, V_2, V_5, and V_6, where the T-P interval following a cycle was on the same horizontal level as the T-P interval preceding the cycle. The incidence of an isoelectric RS-T junction was as follows: in Lead V_1, 88 per cent; in V_2, 69 per cent; in V_5, 88 per cent; and in Lead V_6, 92 per cent. An elevation of 0.5 to 1.5 mm. was found three times in Lead V_1, thirteen times in V_2, once in V_5, and twice in Lead V_6. An elevation of 2 mm. was present in Lead V_2 of one case, this constituting the

sole instance of displacement exceeding 1.5 millimeters. In all cases with RS-T elevation, the RS-T segment and T wave were normal in shape. An RS-T depression of 0.5 to 1.0 mm. appeared to be present in one or more precordial leads of six cases. The apparent RS-T depression in each case could be ascribed to one of the following factors: (1) a prominent auricular T wave, as in Leads V_4 and V_6 of Fig. 2, *B*, which should be suspected when the P wave is tall and is recognized from the presence of a corresponding depression in the interval between the end of the P and the onset of the QRS; (2) the presence of a tachycardia sufficient to cause superimposition of the P wave on the antecedent T and thereby prevent the usual diastolic return of the string to the isoelectric line, as in Fig. 2, *F* and *I*. When a large auricular T wave coexists with tachycardia, a very pronounced pseudodepression of the RS-T junction may occur, as exemplified by Fig. 2, *G*. The apparent depression of the RS-T junction in Leads V_4 and V_6 of this case may be explained partly by the fact that the P wave begins before the T is completed and partly by the presence of a large auricular T wave, which may be seen between the end of the P and the onset of the QRS. This interpretation was borne out by the negative autopsy findings in this patient.

Contour of RS-T Segment.—The tracing may immediately slope away from the RS-T junction to form the T wave, or it may pursue a horizontal course for a variable period, ranging from 0.02 to 0.16 second. The RS-T segment, in the strict sense of the term, refers to the portion of the tracing between the RS-T junction and the point where the string slopes away from the horizontal. It is often difficult or impossible to demarcate the end of the RS-T segment from the beginning of the T wave and it is unnecessary to do so, since the duration of the RS-T segment is of little clinical significance. More important is the general shape of the tracing between the RS-T junction and the summit of the T wave. The contour of this portion of the tracing is normally related to the direction of the T wave. In the seven cases with inverted T wave in Lead V_1 and in the three cases with inverted T wave in Lead V_2, the portion of the tracing between the RS-T junction and nadir of the T wave described a curve with upwardly directed convexity. In 92 per cent of the leads with upright T, this segment described a curve with upwardly directed concavity and in the remainder, this segment sloped straight upward to the summit of the T. Loss of the customary curvature was associated with tachycardia and was not due to digitalis in any case.

T wave was subject to considerable variation in Lead V_1. It was upright in sixteen cases, isoelectric in two, and inverted in seven. The deepest negative T wave in this lead was 2 mm. in amplitude. The T wave in Lead V_2 was upright in forty-nine cases and exceeded an amplitude of 5 mm. in six of these. Three women, aged 19, 31, and 45 years, had inverted T waves in V_2, measuring 1.0, 2.0, and 1.0 mm., respectively (Fig. 1, *J*). It was noteworthy that two nodal premature beats occurring in Lead V_2 of the 31-year-old woman showed a comparable QRS, but an erect T wave. The T wave was upright in Leads V_3, V_4, V_5, and V_6, except in two cases. One of these had an isoelectric T wave in

Lead V_3, occurring as a transitional phenomenon between an inverted T_2 and upright T_4 (Fig. 1, *J*); the other had an isoelectric T wave in Lead V_6 associated with low voltage of the QRS, but a low upright T wave in Lead V_5. The T wave was characteristically smooth in contour in precordial leads, but may be slightly notched in the leads at the transitional zone. The U wave was usually visible when the heart rate was below 100 per minute and was upright in direction.

DISCUSSION

Factors Governing the Form of the QRS in Direct Leads and in Precordial Leads.—Since the findings obtained by multiple direct leads from the epicardium of animals constitute the basis for the utilization and interpretation of multiple precordial leads in humans, a brief résumé of present concepts as to the mechanism of ventricular activation in relation to formation of the QRS will be given as an introduction to the discussion of our studies. The following summary is based principally on the work of Wilson and associates.[2-5]

The ventricular wall is normally set into activation by impulses distributed through the Purkinje network. After arrival at the subendocardial layer, the impulse passes centrifugally toward the epicardium at a rate of approximately 400 mm. per second, and successively activates each responsive muscle cell in its pathway. As the impulse reaches a given cell, it produces a sudden decrease in the impedance of the cell membrane, accompanied by an abrupt drop in electromotive force across this membrane. The cell undergoing excitation becomes negative in respect to the resting cells superficial to it and current flows from points just ahead of the impulse into the cell just behind it. The negative potential of the cell undergoing activation is transmitted backward through the intervening deeper layer of myocardium into the ventricular cavity and the positive potential of the resting muscle ahead of the advancing impulse is transmitted to the epicardium and chest wall.

An exploring electrode attached to the epicardium and connected with a sensitive galvanometer will register a positive potential as soon as the impulse reaches and starts to activate the subendocardial muscle directly beneath. With the galvanometric connections now in use, this results in an R wave, which continues upward until the arrival of the impulse at the epicardial surface, at which time the potential of the exploring electrode suddenly falls, as manifest by a precipitous downstroke called the intrinsic deflection. Therefore, the ascending limb of the R wave of direct leads is primarily a record of positive potential referred to the epicardial surface from electromotive forces created by the activation of the underlying wall, whereas the precipitous descending limb reflects the abrupt disappearance of these forces after arrival of the impulse at the epicardial surface. The time interval from onset to peak of the R wave and the amplitude of the R wave vary with the thickness of the ventricular wall beneath the exploring electrode, and are significantly less in direct leads from the relatively thin normal right ventricle than in direct leads from the relatively thick normal left ventricle.

Impulses distributed through the Purkinje system start to penetrate the interventricular septum and adjacent anterior wall of the ventricles a short time prior to their arrival at the lateral and posterior walls of the left ventricle. During this brief interval, negative potentials referred to the cavity from activation of septum and anterior wall will be transmitted through the as yet unactivated lateral and posterior walls, to be recorded through an overlying exploring electrode as an initial downward deflection, or Q wave. As soon as the impulse reaches and starts to activate the muscle directly beneath the electrode on the lateral or posterior wall, an abrupt reversal in the polarity of the exploring electrode will occur and the Q wave will be replaced by an R. If activation is still in progress in some more remote portion of the ventricle after its completion in the region to which the exploring electode is attached, the negative cavity potentials will be transmitted through the completely depolarized wall to the surface, causing the intrinsic movement to continue downward below the isoelectric line as an S wave. Hence, the Q wave will be absent in records from portions of the wall that are first to become activated (the anterior wall of both ventricles adjacent to the septum) and normally will be deepest and broadest in records from portions which are last to become activated (lateral and posterobasal wall of left ventricle). On the other hand, the S wave will be deepest in tracings from portions of the wall where activation is completed first (normally in leads from the right ventricle) and will be absent in tracings from portions of the wall where activation is completed last (lateral and posterobasal walls of left ventricle).

The QRS pattern recorded through a direct epicardial lead will, therefore, depend upon the amount of responsive muscle in the subjacent ventricular wall and the time of onset and completion of its activation in reference to other portions of the ventricles. With defective conduction in one ventricle, the time interval from onset to peak of R is lengthened in leads over that ventricle, whereas the S wave is exaggerated in leads over the opposite ventricle. Abrupt changes in QRS are demonstrable when the electrode is moved from a normal to an infarcted segment of ventricle. If the entire wall is infarcted, only a QS complex is registered through overlying direct leads, the R wave being absent because of failure of development of electromotive force in the underlying wall. If only the subendocardial layer is destroyed, the Q wave is abnormally increased and the R diminished due to delayed onset of activation of the residual subepicardial muscle and reduced magnitude of the electromotive force. These examples are sufficient to bring out the advantage of multiple over single direct leads in the evaluation of a given ventricle and in the detection of localized lesions.

The potential variations of a precordial electrode are dominated by a much larger segment of ventricular wall than those of a direct lead because of the larger electrode employed for precordial than for direct leads and because of the greater distance from the heart. Nevertheless, comparison of tracings obtained by precordial leads with those obtained by direct leads from the subjacent epicardium ordinarily reveals a fairly close correspondence in general contour and in the relative duration and amplitude of the individual components

of the QRS complex. Tracings obtained by precordial leads are lower in voltage and show a less precipitous downstroke following the peak of the R. This downward movement is, therefore, more appropriately designated as an intrinsicoid deflection. The fairly close correspondence between direct and precordial leads obtains as long as the segment of ventricular wall beneath the exploring electrode is more or less uniform in thickness and in electrophysical activity, as in normal hearts, ventricular hypertrophy, bundle branch block, and so forth, but would not obtain in the presence of a very small myocardial lesion confined to only a portion of the area covered by the precordial electrode. Thus, with the foregoing limitations the demonstrated relationships of the QRS pattern of direct leads to the underlying myocardium in animals can be applied to the interpretation of multiple precordial leads in humans.

When the heart is in normal position, leads from precordial points V_1 and V_2 correspond roughly to direct leads from the epicardial surface of the right ventricle, whereas tracings made at Positions V_5 and V_6 correspond roughly to direct leads from the anterolateral surface of the left ventricle. The time interval elapsing from onset to peak of R wave in Leads V_1 and V_2 is an approximate measure of the time required for the passage of the impulse from the endocardial to epicardial surface of the anterior wall of the right ventricle, whereas the corresponding measurements in Leads V_5 and V_6 are an approximate index of the time required for activation of the anterolateral wall of the left ventricle. The relative amplitude of the R waves in Leads V_1 and V_2 on the one hand, and in Leads V_5 and V_6 on the other hand, serve as a rough index of the relative electromotive forces developed in the activation of the right and left ventricles, respectively. A minimum of two leads over each ventricle is desirable as a basis of comparison.

As the electrode is shifted from right ventricular position V_1 to left ventricular position V_5, the normal electrocardiogram will show a progressive increase in the amplitude of the R wave and the time interval from the onset to the peak of the R, along with a progressive decrease in the amplitude of the S wave. This reflects the normal increase in thickness of ventricular wall as one moves from the anterior wall of the right ventricle to the lateral wall of the left. Small infarcts may result in abnormal increase in Q and reduction of R in a limited zone, amounting to little more than the diameter of the electrode. Thus, multiple precordial leads provide valuable information both for comparison of the two ventricles and for detection of localized lesions. The specific findings in this series of proven normal subjects remain for discussion.

Duration of QRS.—The average QRS interval of 0.078 second was identical with that found by McGinn and White[22] in the standard leads of a group of one hundred normal adults. The upper limit of 0.098 second for the QRS interval is in accord with the findings of Wilson and Herrmann,[23] which were based on measurements of the standard leads of forty-nine autopsied cases. On the other hand, in virtually every large series in which the presence of a normal heart was established by physical and roentgen examination rather than by autopsy, a few cases have been encountered in which the QRS interval in the

standard leads amounted to 0.11 second or more.[24-28] The higher range than in our series cannot be explained by the difference in leads selected, since measurements of QRS duration in precordial leads equal or slightly exceed measurements in standard leads, except in the presence of a localized conduction defect in the posterior ventricular wall. The fact that the QRS duration was confined within limits of 0.06 to 0.10 second in our series may be due merely to chance, operating in a relatively small group of cases. A larger series of electrocardiographic-autopsy correlations is needed to verify the occurrence and to determine the incidence of QRS intervals of 0.11 second or more in cases proven to have normal hearts by post-mortem examination.

Wilson and Herrmann[23] subdivided their cases according to ventricular weight and thickness of the left ventricle and noted that the mean QRS interval lengthened with increase in mean ventricular weight and thickness, but found a number of individual exceptions to these generalizations. They found an average QRS interval of 0.0649 second in cases with a ventricular weight below 150 grams, 0.0699 second for ventricular weights between 150 and 200 grams, and 0.0805 second for those exceeding 200 grams. It must be borne in mind that the figures represent weights of the ventricular segment only and that the group above 200 grams included cases of left ventricular hypertrophy. This probably accounts for the greater spread of values for QRS duration in the series of Wilson and Herrmann than in the cases reported in this communication. Comparison of individual cases in our series likewise revealed no consistent relation between QRS duration and ventricular weight. There was a trend toward slight lengthening of mean QRS duration with increase in mean cardiac weight, as shown by an average QRS interval of 0.077 second in hearts weighing less than 250 grams, 0.079 second in those between 250 and 300 grams, and 0.081 second in those weighing from 300 to 350 grams. These differences are not statistically significant.

Time of Onset of Intrinsicoid Deflection.—Kossmann and Johnston[29] obtained Leads V_1, V_2, V_3, V_4, and V_5 on thirty medical students with hearts which were normal to clinical and roentgen examination, and determined the time of onset of the intrinsicoid deflection with reference to the beginning of the QRS in the simultaneously taken standard Lead I. Our measurements, which were made from the beginning of the QRS to the onset of the intrinsicoid deflection in Leads V_1, V_2, V_5, and V_6, corresponded closely with their findings. For example, the interval preceding the intrinsicoid deflection in Lead V_1 averaged 0.017 second in their cases and 0.014 second in our series. Corresponding measurements in Lead V_2 were 0.019 second and 0.018 second. Their average in V_5 of 0.034 second was greater than our value of 0.030 second in this lead, but was similar to our finding of 0.034 second in Lead V_6. Their longest measurement was 0.055 second and was obtained in Lead V_4, whereas ours was 0.051 second and was found in Lead V_5. The maximal time interval from onset of QRS to peak of R could not be correlated with heart weight in our cases. Their observation that the time of onset of the intrinsicoid deflection was invariably later in leads from the left than in leads from the right side of the precordium

was confirmed in this study. The difference averaged 0.0194 second in their cases and 0.0192 second in our twenty-five cases in which measurements were available in Leads V_1, V_5, and V_6. The greatest difference in measurements was found to be 0.030 second in both series and the smallest was 0.008 second in their series and 0.003 second in ours. Since the onset of the intrinsicoid deflection marks the arrival of the impulse at the epicardial surface beneath the exploring electrode, the longer intervals in leads over the left than in leads over the right ventricle would be expected in view of the normally greater thickness of the left ventricular wall.

The anticipated correlation between the time of onset of the latest intrinsicoid deflection and cardiac weight was not borne out in this study; however, when the time interval from the onset of the R to the peak of the R in Leads V_6 or V_5 was plotted against heart weight, a trend was found toward a slightly longer duration of the R wave with increasing cardiac weight. Since the interval elapsing from onset of R to its peak is an index of the time required for the impulse to pass from the endocardial to the epicardial surface of the segment of wall beneath the electrode, it is not surprising to find that this measurement is better correlated with cardiac weight than the time interval from the beginning of the QRS to the start of the intrinsicoid deflection. It is noteworthy that the longest measurement from the beginning to the peak of R in this series of normal hearts was 0.037 second, and that the value was below 0.035 second in all but five of the cases. The duration of the R wave was invariably greater in leads over the left than in leads over the right ventricle, the average difference being 0.013 second.

Direction of Initial Deflection of QRS.—The variable findings in Lead V_1 among normal subjects may be in part attributable to differences in the relation of the electrode to the underlying cardiac chambers. The electrode at Position V_1 may lie over the anterolateral wall of the right ventricle, in which event an initial R wave derived from activation of the subjacent right ventricular wall would be expected. In some cases, however, the electrode in Lead V_1 lies over the right atrium, and thus faces toward the atrioventricular orifices and is dominated by the potential variations of the ventricular cavities. Under such circumstances, the QRS may consist solely of a QS complex or may show a small initial R from momentary positivity of the right ventricular cavity. This may be due either to a slightly earlier onset of activation of the left than of the right half of the septum,[30] or to greater magnitude of electrical forces developed in the left than in the right side of the septum. This probably explains why an RS complex is a much more common normal finding in Lead V_1 than a QS complex. It should be emphasized that an initial Q followed by an RS does not occur as a normal finding in Leads V_1 or V_2.

A QS complex may be found in both Leads V_1 and V_2 when the heart is displaced backward and to the left, thereby bringing the electrode into closer proximity to the right atrium. Evidence of such displacement in Case B of Fig. 1 is afforded by the shift in transitional zone to the left and by the prominent late R wave in Lead aV_R.[31] Before considering the QS in both Leads V_1 and

V_2 as a rare normal variant, it is advisable to take additional leads from the right anterior chest. If the QS complexes in Leads V_1 and V_2 are due to displacement of the heart backward and to the left, a similar deflection should be obtained in Lead V_{3R} and in other leads from the right anterior chest wall. On the other hand, if the QS complex in Leads V_1 and V_2 is a remnant of an old anteroseptal infarction, a small initial R wave should be demonstrable in Lead V_{3R} or in Lead V_E. The Q wave which may be found normally in leads from the left axilla is merely an expression of the slightly later onset of activation of the lateral wall of the left ventricle than the septum and adjoining anterior wall. The normal Q in Leads V_4, V_5, and V_6 is brief in duration and small in amplitude. The time interval from onset to nadir should fall within a range of 0.005 to 0.02 second and the amplitude should be less than 25 per cent of that of the R wave in the same lead. When the time interval from onset to nadir exceeds 0.02 second and the amplitude exceeds 25 per cent of that of the R wave in the same lead, the Q wave is probably abnormal and most likely the result of infarct or fibrosis of the subendocardial portion of the underlying wall.

Location of transitional zone and zones of reference of right and left ventricular potentials is subject to considerable variation, even when the heart is normal in size. Individual variations are traceable to differences in the shape of the chest and in the position of the heart. In this study, as in that of Kossmann and Johnston,[29] the transitional zone was most commonly found between Positions V_2 and V_4, leads to the right being dominated by potential variations of the epicardial surface of the right ventricle and leads to the left, by potential variations of the epicardial surface of the left ventricle. The QRS recorded at the transitional zone may normally exhibit notching or slurring,[29,32] probably due to greater admixture of potential variations from the two ventricles. Kossmann and Johnston[29] found that a notch on the descending limb of the R wave was practically synchronous with the onset of the intrinsicoid deflections in leads further to the left, whereas a notch on the ascending limb of the R wave was practically simultaneous with the onset of the intrinsicoid deflection in leads further to the right.

Whenever the transitional zone is located somewhere between Positions V_2 and V_5, a minimum of two out of the six precordial leads will be dominated by the potential variations of each ventricle, which generally makes the precordial electrocardiogram adequate for interpretation. In rare instances the transitional zone may be displaced to the right of Position V_2 or to the left of Position V_5. This may cause confusion unless additional leads are taken further to the right and left, as illustrated by the patient whose tracing is shown in Fig. 1, *F*. In Leads V_1 and V_2 the R wave is relatively large in proportion to the S, a finding which would suggest right ventricular hypertrophy if the transitional zone were located in its usual position. However, the fact that the $\frac{R}{S}$ ratio in Leads V_1 and V_2 is comparable to that in leads further to the left would suggest that Leads V_1 and V_2, like V_3, V_4, V_5, and V_6, reflect chiefly the potential variations of the left ventricle. The upright T wave of normal contour in V_1 and V_2 constitutes

further evidence against the presence of right ventricular hypertrophy. The patient whose tracings are shown in Fig. 1, *F* died before additional leads could be obtained, but autopsy revealed a normal right ventricle, thereby excluding right ventricular hypertrophy as a cause of the pattern in Leads V_1 and V_2 and lending indirect support to the supposition that the transitional zone was displaced to the right of the sternum. The foregoing case was discussed in some detail to emphasize the importance of obtaining additional precordial leads further to the right and left when the tracings obtained at the six customary points are more or less constant in form.

Voltage of QRS.—The average amplitude of the R wave in precordial Leads V_1, V_2, V_3, V_4, and V_5 of this series was approximately half that found by Kossmann and Johnston[29] in corresponding leads, in spite of the fact that the time interval during which the R wave was registered was almost identical in the two series. These differences are attributable, at least in part, to extrinsic causes. A greater loss of potential through the chest wall would be expected in our cases, since 60 per cent were in the age group over fifty years, in which emphysema is common, and 30 per cent were women, whose soft tissues are generally thicker than those of men due to the presence of the breasts.

Determination of the maximal amplitude of the R wave in the six precordial leads is of limited diagnostic value. Although R waves of large amplitude tend to be associated with ventricular hypertrophy, voltages in the same range may be obtained in some normal individuals, especially in young persons with thin chest walls. However, high voltage of the R wave, when accompanied by lengthening of the time interval between its onset and peak to 0.04 second or more, is highly significant and will be discussed in greater detail in a future communication.

R waves of low voltage (less than 0.7 mv. in all six precordial leads) should arouse suspicion of a myocardial lesion,[33] but were found in four normal subjects in this series. The only case in which the R wave was less than 0.5 mv. in all precordial leads had marked edema of the chest wall from superior vena caval obstruction produced by a mediastinal lymphosarcoma. The low voltage in one case (Fig. 1, *D*) could be attributed to vertical position of the heart, the forces derived from left ventricular activation being directed more downward than anteriorly, producing a tall R wave in Leads aV_F, II, III. The low voltage of the R in the two remaining cases (Fig. 1, *A* and *E*) could be ascribed to backward displacement of the apex, a greater portion of the forces derived from left ventricular activation being directed backward, causing a late R wave in Lead aV_R and a late S wave (and consequent reciprocal reduction in the R wave) in Leads V_4, V_5, and V_6.

Relative Amplitude of R and S Deflections in Each Precordial Lead.—As the electrode was moved from Positions V_1 or V_2 toward the left, a progressive increase in the R wave and reciprocal decrease in the S wave was found in every case, thereby confirming the observations of Kossmann and Johnston.[29] The location of the maximal R was most commonly in Lead V_4, but varied from V_3 to V_6, depending upon the configuration of the thorax and position of the heart.

When the electrode was moved from Position V_4 to V_5 and then to V_6, the most common finding was a progressive decrease in amplitude of the R wave due to increasing distance between the electrode and the left ventricle. The reverse relationship (that is, increasing amplitude of R wave) may occur as a normal variant when the heart is in vertical position and when the apex is displaced backward or to the left.

The S wave attained its maximal amplitude in leads over the right ventricle, sometimes in V_1, but more often in V_2. The S wave recorded in these leads was derived from activation of the outer wall of the left ventricle. As soon as the septum and right ventricular wall have become completely depolarized, the negative potentials referred to the left ventricular cavity from the continuing activation of the outer wall of the left ventricle are transmitted to electrodes overlying the right ventricle, to be registered as an S wave in these leads. There are at least two factors governing the relative amplitudes of the S waves in Leads V_1 and V_2. The fact that the peak of the R wave is attained slightly earlier in V_1 than in V_2 allows a slightly longer interval for transmission of negative left ventricular cavity potentials to the electrode at Position V_1 than to that at V_2, and thus tends to make the S wave deeper at Position V_1. The greater distance from the left ventricular cavity to Position V_1 tends to cause a greater decrement in potential, and thus tends to make the S wave at V_1 smaller than that at V_2. The resultant finding depends upon the balance between these two factors.

RS-T Segment.—An elevation in the RS-T junction of 0.5 to 1.5 mm. above the isoelectric line was a fairly common finding in this series, and an elevation of 2.0 mm. was present in one case. In view of the fact that normal elevation of the RS-T junction is associated with an abruptly rising RS-T segment and tall upright T wave, it is probable that the electromotive forces developed during repolarization have reached sufficient magnitude by the end of the QRS to account for the upward displacement of the RS-T junction. An elevation of the RS-T junction may be considered within normal limits if the displacement does not exceed 2.0 mm., and provided that the RS-T segment immediately begins to rise above the junction in an arc with upward concavity to end in a tall upright T wave. Depression of the RS-T junction is very rare in the precordial leads of normal electrocardiograms and should be regarded as abnormal if it amounts to 0.5 mm. or more, provided pseudodepression from tachycardia or an auricular T wave are excluded.

T Wave.—Suarez and Suarez, Jr.,[34] took electrocardiograms on thirty-one normal women between the ages of 19 and 45 years, and found inversion of the T wave in Lead V_2 in four cases and in Lead V_3, as well, in one case. They attributed the inverted T waves to the persistence of the juvenile pattern into adult life. In a study of the CF leads on young adults with clinically normal hearts, Littmann[35] found that inversion of the T wave in Leads CF_2, CF_3, and CF_4 was more common among colored than white subjects and more frequent in women than in men. The T wave in Lead V_2 was upright in forty-nine of our cases and was inverted in one white girl, 19 years of age, and in two Negro women, 31 and 45 years of age. The T wave in Lead V_3 was isoelectric in the latter patient, but

was upright in the remaining fifty-one. Since the hearts were normal at autopsy and no cause for the T wave inversion was demonstrable, it was regarded as a normal variant, perhaps due to the persistence of the juvenile pattern. Inversion of the T wave in Leads V_4, V_5, and V_6 was not found in this series or in normal adults studied by Suarez and Suarez, Jr., and by Kossmann and Johnston. Flattening of the T wave in Lead V_6 is probably within normal limits when the QRS in this lead is low in voltage, but normal in configuration.

SUMMARY

1. Wilson precordial leads have been correlated with autopsy findings in a group of 1,000 cases. In this communication, an analysis is presented of the precordial electrocardiograms of fifty-two patients whose hearts were considered normal by gross and microscopic examination.

2. The P wave was consistently upright in Leads V_4, V_5, and V_6 and varied from erect to diphasic in Leads V_1, V_2, and V_3, depending upon the position of the electrode in reference to the right atrium.

3. The total QRS interval and the duration of each component phase were determined in Leads V_1, V_2, V_5, and V_6 with aid of a Cambridge measuring device. The average QRS interval was 0.078 second and the upper limit in this series was 0.098 second. There was a trend toward slight lengthening of QRS duration with increasing cardiac weight.

4. A QRS complex was found in both Leads V_1 and V_2 in two cases, but was not present in leads further to the left. An initial Q with succeeding R was not found in leads over the right ventricle, but was present in at least one lead over the left ventricle in approximately two-thirds of the cases. This Q wave was brief in duration, reaching its nadir within 0.02 second, and was small in magnitude, amounting to less than 25 per cent of the amplitude of the succeeding R wave.

5. The interval elapsing from the onset of the R wave to its peak was taken as an index of the time required for the impulse to pass through the segment of ventricular wall beneath the exploring electrode. The time interval from onset to peak of R was invariably minimal in Lead V_1 and increased progressively in leads further to the left to reach a maximum in Leads V_5 or V_6. The significantly longer duration of the R wave in leads over the left than in leads over the right ventricle was in keeping with the normal difference in thickness of their respective walls. There was a trend toward a slightly greater duration of the R wave in Lead V_6 with increasing ventricular weight. As the electrode was moved from positions over the right to positions over the left ventricle, a progressive increase in the amplitude of the R wave and a reciprocal decrease in the S wave was found in every case. Low voltage R waves that were less than 7 mm. in height in all six precordial leads were found in four normal subjects in this series. Normal variations in the position of the transitional zone and form of QRS complexes recorded in this zone are illustrated and discussed.

6. An elevation of the RS-T take-off of 0.5 to 2.0 mm. may be considered as a normal variant, provided that the tracing immediately begins to rise above

the RS-T junction in an arc with upward concavity to end in a tall upright T wave. Depression of the RS-T junction is very rare in the precordial leads of subjects with normal hearts and should be regarded as abnormal if it amounts to 0.5 mm. or more, provided that pseudodepression from tachycardia or a prominent auricular T wave are excluded.

7. An inverted T wave was a frequent finding in Lead V_1 and was present in Lead V_2 in three normal women, 19, 31, and 45 years of age, respectively. The T wave was upright in Leads V_3, V_4, V_5, and V_6 except in two subjects, one of whom had an isoelectric T in V_3 associated with an inverted T wave in Leads V_1 and V_2. The other had an isoelectric T in Lead V_6 associated with low voltage of the QRS.

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VARIATIONS IN THE FIRST HEART SOUND IN COMPLETE A-V BLOCK

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GRIFFITH[1] is generally credited with having first noted the marked variation in intensity of the first heart sound in patients with complete atrioventricular block, though Orias and Braun-Menendez[2] give credit for this observation to Straseschko. Griffith, using polygraphic records, concluded that intensification of the first sound resulted from ventricular contraction during auricular systole. The influence of varying time relationships between auricular and ventricular contractions upon the intensity of the first heart sound has been carefully studied by Wolferth and Margolies.[3] They found that the first sound was most intense when the P wave preceded the QRS complex by 0.10 to 0.20 second, and that on both sides of this time interval there was diminution in the amplitude of the sound. This observation suggested to them that the position of the mitral valve leaflets at the beginning of ventricular contraction was an important factor in determining the loudness of the first sound. They felt that when the leaflets were wide open slight regurgitation might occur into the auricle, preventing a rapid rise in intraventricular tension; conversely, if the ventricular contraction occurred at a time when the leaflets were nearly closed, there might be a little or no interference with the rise in ventricular tension, thus leading, they thought, to a louder sound. Their deductions from application of the animal experiments of Dean[4] led them to the conclusion that loud first sounds were produced when the mitral leaflets were nearly closed.

Dock[5] has presented experimental evidence to support his belief that the first heart sound is entirely valvular in origin, and more recently[6] has disputed the contradictory conclusions of Smith and associates.[7]

The present paper is substantially a repetition of the work done by Wolferth and Margolies; however, we used a different type of equipment, and have reached somewhat different conclusions. Six patients with complete A-V block, and with clinically normal A-V valves, have been studied. The heart sounds were recorded during expiration with the Electrocardiograph-Stethograph.* The amplitude in millimeters of the vibrations produced by the first heart sound was measured and graphed to show its time relationship to the preceding P wave of the simultaneously recorded electrocardiogram. Wiggers[8] accepts the amplitude

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of the sound vibrations as a satisfactory index of their loudness. Sounds associated with a short R-P interval have been graphed twice; that is, also to show the long P-R interval of the preceding P wave.

The absolute amplitudes of the first heart sounds are comparable only in individual records, since the position of the microphone, the position of the patient, the tension of the elastic band holding the microphone, and the exact degree of amplification affect the height of the vibration in the sound record.

CASE REPORTS

CASE 1.—P. S., a student nurse, 19 years of age, was found to have complete atrioventricular dissociation when the members of her class were subjected to electrocardiographic study for another purpose. She had had no symptoms, though she had noted that her pulse rate had been about 50 per minute since February, 1945; she also had noted that her pulse rate increased slightly with exercise. She had had a severe sore throat at the age of 10 years and her left knee was painful and stiff for a period of two days two years later.

The blood pressure was 112/72. The cardiac rhythm was slightly irregular with marked variation in the intensity of the first heart sound. The pulmonary second sound was reduplicated. A very faint systolic murmur could be heard over all valve areas. The heart was normal in size to percussion and on fluoroscopic examination. The electrocardiogram showed complete atrioventricular block with supernormal conduction of some atrial impulses; intraventricular conduction was normal.

Fig. 1, *A*, shows the variations in amplitude of the first heart sound as related to the P-R interval. The atrial complexes with a P-R interval of about 0.35 to 0.43 second were those that were conducted to the ventricles. Injection of 1 mg. of prostigmine caused the disappearance of conducted beats, presumably by vagal depression of the conducting tissues; Fig. 1, *B*, illustrates the curve obtained after the injection of prostigmine. Injection of either atropine or epinephrine facilitated conduction so that there was 1:1 conduction, though the P-R interval was prolonged under these circumstances to 0.35 second.

In Fig. 1, *A*, the amplitude of the first sound fell rapidly when the P-R interval was as short as 0.43 second, and sounds of minimal intensity were recorded at P-R intervals of 0.40 to 0.24 second. The intensity rose rapidly with shorter P-R intervals and reached a maximum at 0.11 second. It then fell off to a moderate value at about 0.04 second and rose again slightly as the P wave coincided with, or followed shortly after, the R wave.

The curve obtained after prostigmine (Fig. 1, *B*) differed only in the absence of conducted beats. Hence, the points expressing loudness of the first sound are lower when the P-R interval is shorter than 0.60 second, and are lowest at 0.21 second. Those for shorter P-R intervals are qualitatively identical with those in Fig. 1, *A*, though there happens to be fewer points in the region where the P-R interval was less than 0.09 second.

In Fig. 1, *A*, the curve rises acutely as the P-R interval exceeded 0.40 second. All points just above 0.35 second are associated with conduction of the P wave, and, hence, with a somewhat shorter R-R interval. This area should be compared with the corresponding area of Fig. 1, *B*. We have not attempted to evaluate the effect of varying R-R intervals.

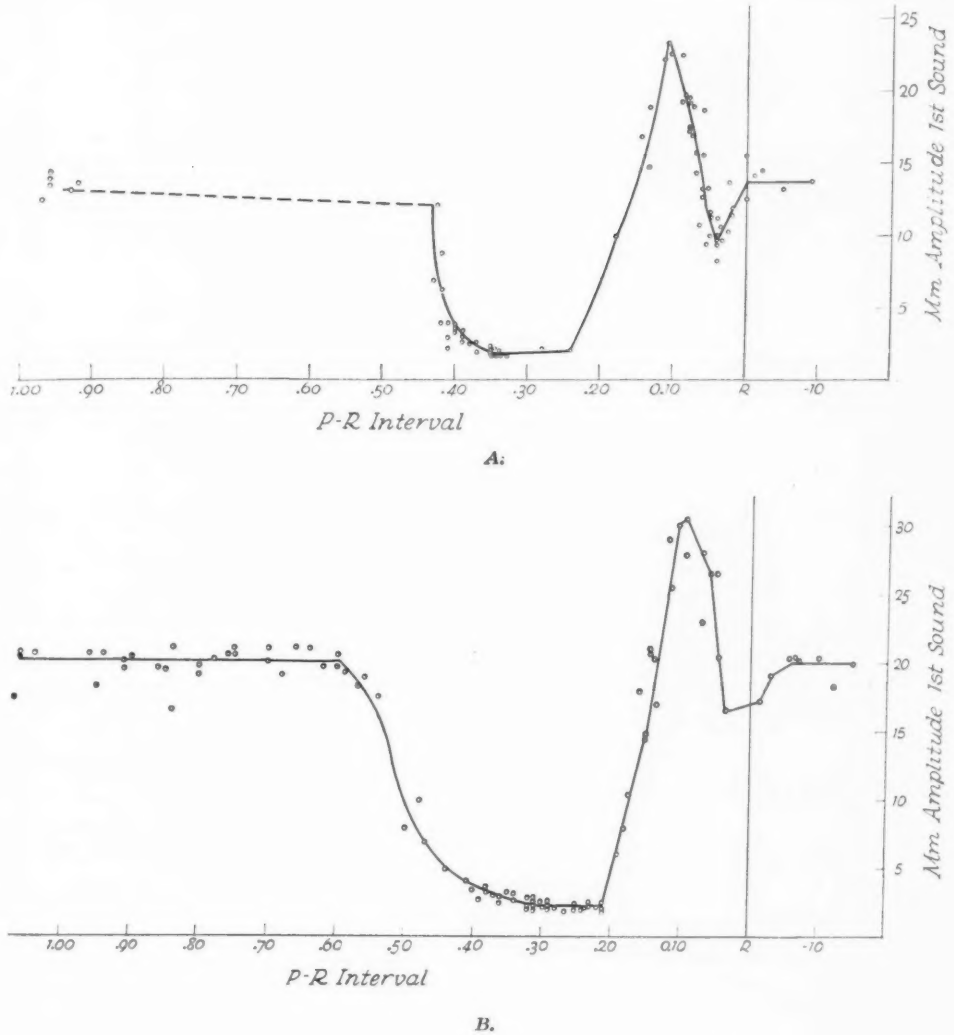

Fig. 1.—*A*, Relationship of amplitude of first heart sound to preceding P-R interval. Case 1. *B*, Same as *A* after injection of prostigmine.

CASE 2.—J. C. S., a white man 25 years of age, had been under observation elsewhere since childhood for congenital heart disease. He had a systolic thrill and a systolic murmur maximal in the left third intercostal space, considered indicative of an interventricular septal defect. The heart was normal in size and there were no cardiac symptoms. A complete heart block, with normal intraventricular conduction, was present.

Fig. 2 shows the relationship between the amplitude of the first heart sound and the preceding P-R interval. With P-R intervals shorter than 0.54 second, the amplitude of the vibrations produced by the first heart sound diminished and reached a minimum at about 0.25 second. With shorter P-R intervals, the

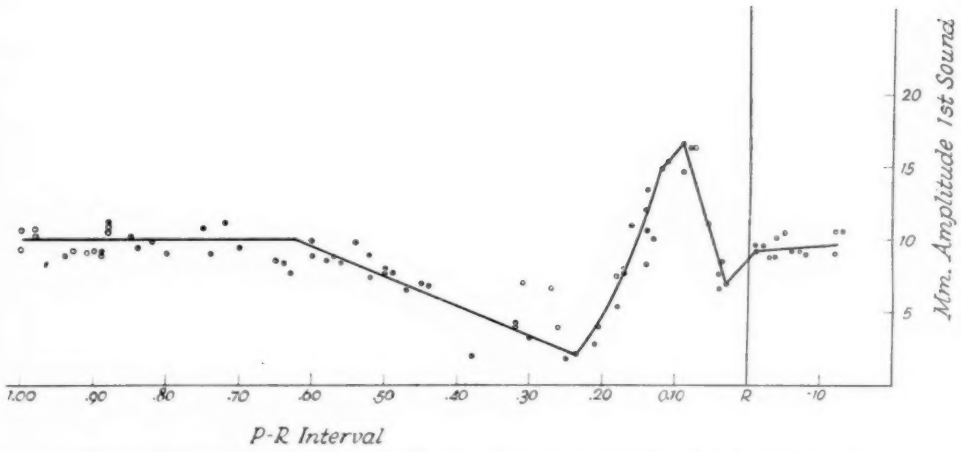

Fig. 2.—Relationship of amplitude of first heart sound to preceding P-R interval. Case 2.

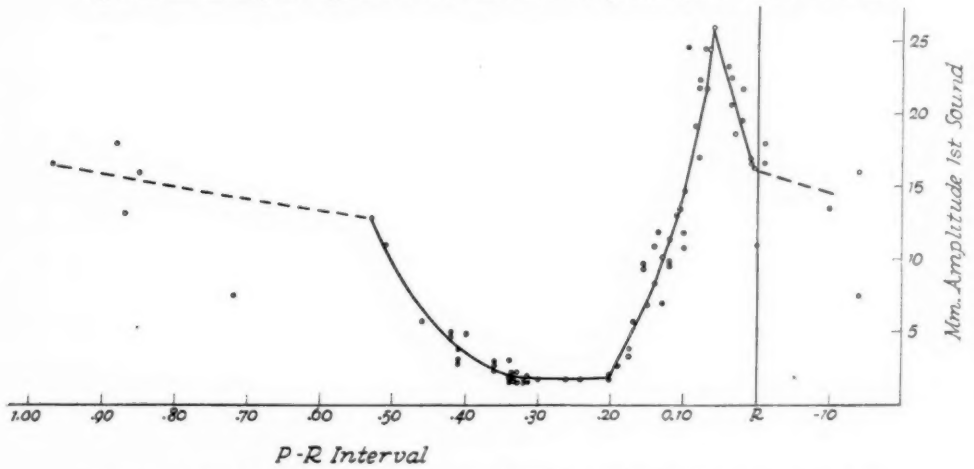

Fig. 3.—Relationship of amplitude of first heart sound to preceding P-R interval. Case 3.

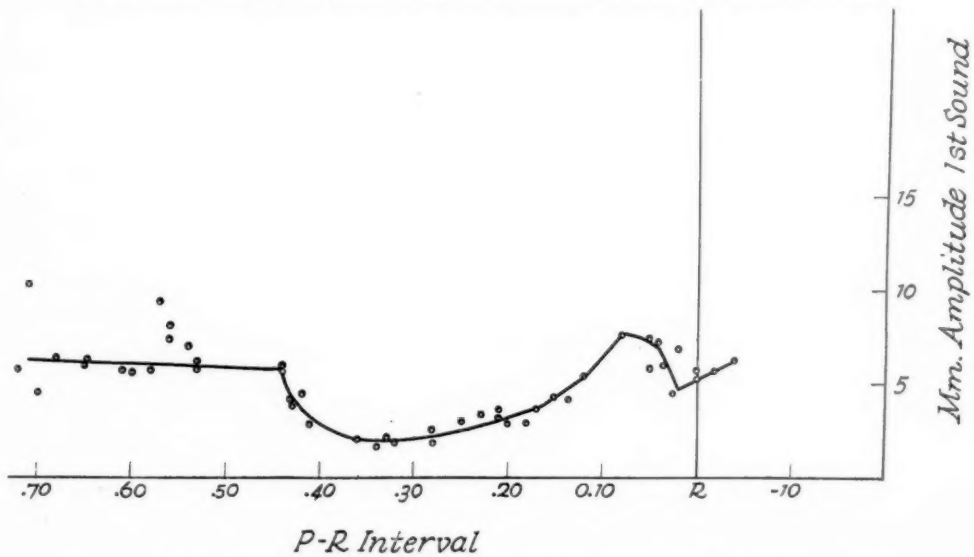

Fig. 4.—Relationship of amplitude of first heart sound to preceding P-R interval. Case 4.

amplitude increased, reaching a maximum value at approximately 0.09 second. A decrease followed with a secondary minimum at 0.04 second, with slightly higher values when the P wave coincided with, or followed shortly after, the R wave.

CASE 3.—L. C., a white girl 9 years of age, was sent to the hospital because of Adams-Stokes seizures. A very slow pulse rate had been noted at the age of 8 months, and syncopal attacks of varying severity and frequency had occurred since that age. These were readily controlled with small doses of ephedrine. The heart was enlarged; the apex was in the sixth intercostal space. A systolic murmur of moderate intensity could be heard at all valve areas, but was loudest at the pulmonary area. The electrocardiogram showed complete atrioventricular block; a left bundle branch block was usually present, but there was considerable variation in the contour of the QRS complexes.

Fig. 3 shows the relationship between the P-R interval and the amplitude of the following first heart sound. Very few points were obtained at P-R intervals greater than 0.53 second, and these were duplicates of instances where a short R-P interval could also be measured. With P-R intervals of less than 0.53 second, the loudness of the first sound diminished, and was at a minimum in the range 0.34 to 0.20 second. When the interval was shorter, the intensity of the sound rapidly increased, reaching a maximum at 0.06 second. It then diminished, with a secondary minimum apparently occurring when the P wave coincided with the R wave.

CASE 4.—M. C., a colored woman 53 years of age, presented herself at the clinic because of vertigo and edema of the ankles. She had experienced no definite syncopal attacks. The blood pressure was 250/150. The heart was dilated, with the apex in the anterior axillary line. There was a moderately loud systolic murmur heard over the whole precordium, loudest in the aortic and mitral areas. The electrocardiogram showed complete atrioventricular block and left bundle branch block. On one occasion transient auricular fibrillation was recorded.

Fig. 4 shows the data obtained in this study. The first heart sounds show, less prominently, the same variations in intensity noted in the preceding cases. The minimum amplitude occurrd at about 0.36 to 0.28 second. This increased as the P-R interval shortened, and was at a maximum at 0.05 to 0.08 second. A secondary minimum occurred when the P-R interval was approximately 0.02 second.

COMMENT

Inspection of the data graphically recorded in the preceding material shows that there is a definite resemblance between the curves of all four cases. Two additional cases showed similar trends, but the points obtained were more widely scattered. Fig. 1, *B* may be assumed to be a fairly typical curve, particularly if it is supplemented by the points in the very short P-R interval range in Fig. 1, *A*.

The other curves are strikingly similar, with one exception. In Figs. 3 and 4, both derived from patients with left bundle branch block, the maximal intensity of the first heart sound definitely falls closer to the R wave by about 0.04 second. The secondary minimum in intensity of the sound in Figs. 1 and 2 occurs at 0.04 second. In Figs. 3 and 4, the corresponding points occur ap-

proximately simultaneously with the R wave. In other words, the presence of a left bundle branch block shifts the curve toward the R wave by about 0.04 second. This seems to agree with the conclusions reached by Wolferth and Margolies[9] in their study of atrioventricular intervals and split first heart sounds. When there is left bundle branch block, the delay in excitation and in contraction of the left ventricle is reflected in the curves we have drawn, since left ventricular contraction is later after the beginning of the QRS complex than normal.

In their earlier paper, Wolferth and Margolies[3] studied seven patients with defective A-V conduction. They related the P-R interval to the loudness of the first sound on a semiquantitative basis, classifying each sound in one of three categories of intensity. It is difficult to compare our measurements with data recorded simply as 1 to 3 plus intensity. Study of the tabulated data of Wolferth and Margolies shows that the maximum intensity of the first sound in their cases varied considerably from P-R intervals of 0 up to about 0.20 second. This at least agrees with our observation that the minimum intensity occurs usually in the range of P-R intervals of about 0.20 to 0.40 second. Attempts at more exact comparison seem fruitless.

Their classic study indicated strongly the vital importance of the position of the mitral leaflets in determining the loudness of the first sound. We believe that our own observations strongly support this opinion. It is, however, an unsettled question as to the exact position of the valve leaflets that produces a faint, or a loud, sound. This uncertainty caused Wolferth and Margolies not to accept valve closure as the most important factor in first sound production. They appear to lean toward the concept that a rapid rise in intraventricular tension, facilitated by already closed valves, produced the loudest first sound. They reasoned that, if the mitral leaflets were in a wide open position at the beginning of ventricular systole, slight regurgitation might occur, thus retarding the development of intraventricular tension and giving rise to first heart sound of relatively lower intensity. In this connection it is interesting to point out that all of our patients had mitral systolic murmurs varying from faint to moderate intensity. However, in the individual patient, there was no noticeable variation in the intensity or duration of the murmurs, either audibly or stethographically. Hence, while mitral regurgitation may have a contributory damping effect on the first heart sound, this effect may be considered consistent for all P-R intervals, and thus would not qualitatively affect the curves shown for our cases.

The only available experimental study of the movement of the mitral leaflets during the cardiac cycle is that of Dean.[4] One of his curves is diagrammed in Fig. 5, *A*, and shows mitral valve movements during auricular systole. There is slight upward movement of the leaflets during the last moments of passive ventricular filling, followed by a sharp downward movement at the time of auricular contraction. The valve leaflets then move toward a position of incomplete closure; this is called auricular closure by Dean. They then drop downward again, but not as far as before.

Since the position of the mitral leaflets would appear to be a vital factor in determining the loudness of the first sound, we have attempted to compare our own data with the curve shown by Dean. Since (1) the amplitude of the vibrations of the first heart sound is clearly related to the interval between auricular and ventricular contraction, as indicated by the P-R interval, and (2) our data are graphed in such a manner that this interval is increased toward the left, it is necessary for comparison to reverse the diagram (Fig. 5, *B*), so that the times after auricular contraction are similarly increased toward the left. If one assumes that the loudest sound is produced when ventricular contraction suddenly tenses the mitral leaflets while they are in the widest open position, the further analysis of our graphs is facilitated by inverting the diagram, so that the position of closure is downward and the open position is upward. One then obtains Fig. 5, *C*, which should be compared with the curves graphed from our data.

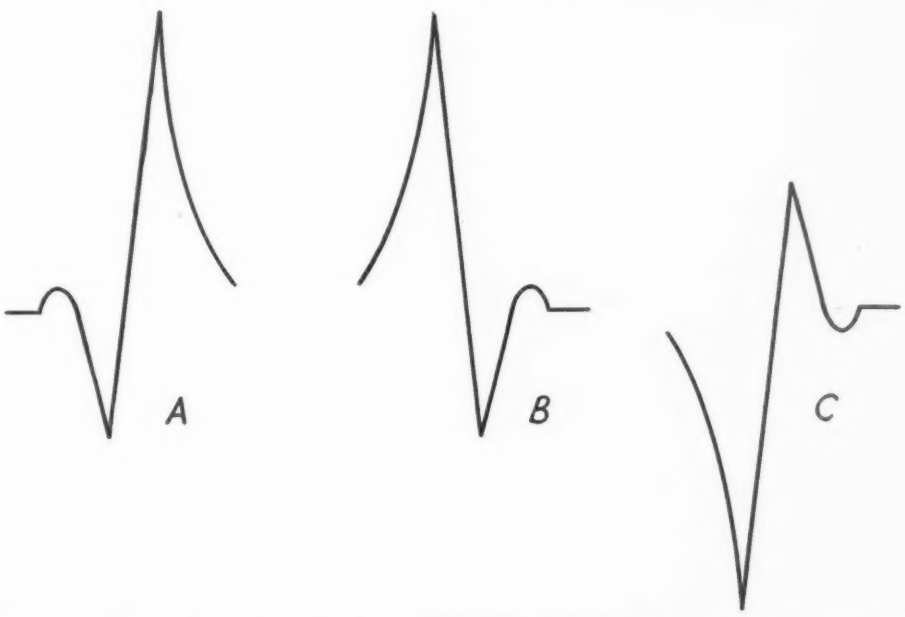

Fig. 5.—Movements of mitral valve due to auricular systole, represented according to Dean (*A*) and applied to our data (*B* and *C*). See text.

There are obviously many fallacies in an attempt to correlate information obtained experimentally from the cat heart with data on the intensity of human heart sounds. It seems to us that Dean's method possibly interfered with valve opening, and favored valve closure; nor is it easy to be certain of his time relationships since his figures do not include a time record. It is striking, however, that with appropriate recasting of his diagrams, figures are obtained which show substantial qualitative and semiquantitative agreement with our own. This agreement appears to support the contention of Dock[5] that the loudness of the first sound depends on the degree to which the valves are open; valves nearly closed produce very faint sounds. This further emphasizes the dominant role

of the valve leaflets in the production of the sound, and minimizes the importance of muscular contraction as a primary factor in the production of the first heart sound.

The weak point in this hypothesis lies in the fact that the exact time-position relationship of the mitral leaflets remains undetermined. Some information may be gleaned from Dean's discussion, but it pertains to mechanical contraction of the heart chambers and mitral valve position. Hence, it cannot be profitably transferred to data associating the electrocardiographic complexes and heart sounds, even though these are directly related to contraction and valve position. In addition, application of time intervals from the cat heart to the human heart might be susceptible to considerable error. Hence, we have felt it futile to attempt to apply Dean's statements as to time to our own observations. It seems certain, however, as Dock[5] has pointed out, that in the P-R interval range up to about 0.20 second, which includes the peak of loudness, the valves must be open rather than closed. This is more certainly true in the narrow range of 0.09 to 0.11 second where maximal sounds occur in those patients without bundle branch block. If this be accepted, the range of P-R intervals just above 0.20 second, where the first sounds are very faint, is that time interval where the valve leaflets are in the position designated by Dean as that of auricular closure.

These questions must await final agreement upon more exact information, in both experimental and human material, on the time-position relationships of the mitral leaflets. Such information should be obtainable by roentgen-kymographic technique in suitable patients, but we have been unable to find that any such study has been recorded.

SUMMARY

Four patients with complete atrioventricular block have been studied stethographically, and the loudness of the first heart sound related to the preceding P wave. Deductions have been drawn which emphasize the importance of vibrations of valvular origin in the production of the first heart sound.

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AN ELECTROCARDIOGRAPHIC PATTERN OF INFARCTION OF THE INTERVENTRICULAR SEPTUM, EXTENDING FROM THE ANTERIOR TO THE POSTERIOR ASPECT OF THE HEART

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THE use of multiple chest leads has enhanced our ability to diagnose accurately the site of myocardial infarction.[1] Anteroseptal location is indicated by significant changes in the leads from the right side of the precordium. These signs, however, are not dependable evidence of involvement of the interventricular septum. They may be also observed when infarction is confined to parts of the anterior wall close to the septum. Similarly, when a Q_3-T_3 pattern is present, infarction of the posterior wall may or may not include a portion of the interventricular septum. There are, however, cases showing a combination of the Q_3-T_3 pattern and significant changes in the leads from the right side of the precordium which suggest infarction of the same stage in the anterior and posterior walls. Wilson and associates,[1] who published such a tracing in 1944, remarked, "We are unable to explain these findings but may point out that apical infarction may give rise to electrocardiographic changes of this sort if the heart were in the vertical position." More recently Wilson and associates[2] published a case of this type in which necropsy revealed a myocardial infarction that extended from the anterior wall through the interventricular septum to the posterior wall of the left ventricle.

In the last few years we have had an opportunity to observe five cases, with necropsy control, whose electrocardiograms showed the Q_3-T_3 pattern and changes in the chest leads significant of anteroseptal infarction. All cases presented a rather identical anatomic finding. The interventricular septum was infarcted throughout between the anterior and posterior aspects of the heart, while involvement of the anterior and posterior walls varied from case to case.

CASE REPORTS

CASE 1.—N. E., a 44-year-old woman, was suddenly seized with precordial pains that radiated to both arms on June 25, 1945. The pain persisted for hours and was accompanied by vomiting. It was followed by rise in temperature and an increase of the white blood count and sedimentation rate. Gallop rhythm was heard over the heart. The blood pressure was 150/108. On the ninth day after the attack of pain, the patient succumbed to cerebral embolism.

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An electrocardiogram (Fig. 1, *A*) was taken seven hours after the onset of the attack of pain. It showed significant Q waves in Leads II and III. QRS was of low voltage in the limb leads; its duration was 0.08 second. The S-T junction was depressed in Lead I and elevated in Lead III. T_3 was dome-shaped. In Leads CF_2 and CF_3 the S-T junction was abnormally elevated and the T wave was high. Tracing *B* (Fig. 1), which was taken three days after *A*, showed progressive changes in limb and chest leads. The duration of QRS was increased to 0.12 second and the tracing showed the pattern of right bundle branch block. The Q deflection was more pronounced in Leads II and III. T_3 had the features of a "coronary T." In Leads CF_2 and CF_3 the S-T junction was still elevated and there was beginning inversion of T.

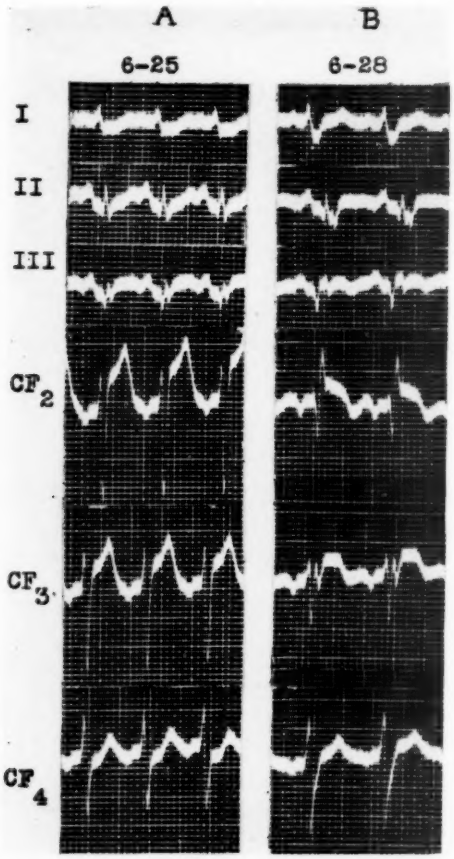

Fig. 1.—Case 1. Extensive recent infarction of the interventricular septum, involving its entire length and extending posteriorly over the apical portion of the left ventricle. The electrocardiograms, taken seven hours and three days, respectively, after the coronary attack, show progressive changes indicative of acute posterior and anteroseptal infarctions.

Progressive electrocardiographic changes in the limb leads pointed to acute posterior wall infarction; those in Leads CF_2 and CF_3 suggested acute infarction of anteroseptal site.

Post-morten examination revealed marked narrowing of the coronary arteries due to arteriosclerosis. The mid-portion of the right coronary artery was occluded by a recent thrombus. A fresh infarction occupied the entire length of the interventricular septum and extended posteriorly over the apical portion of the left ventricle. Both endocardial surfaces of theinterventricular septum were covered with organizing blood clots.

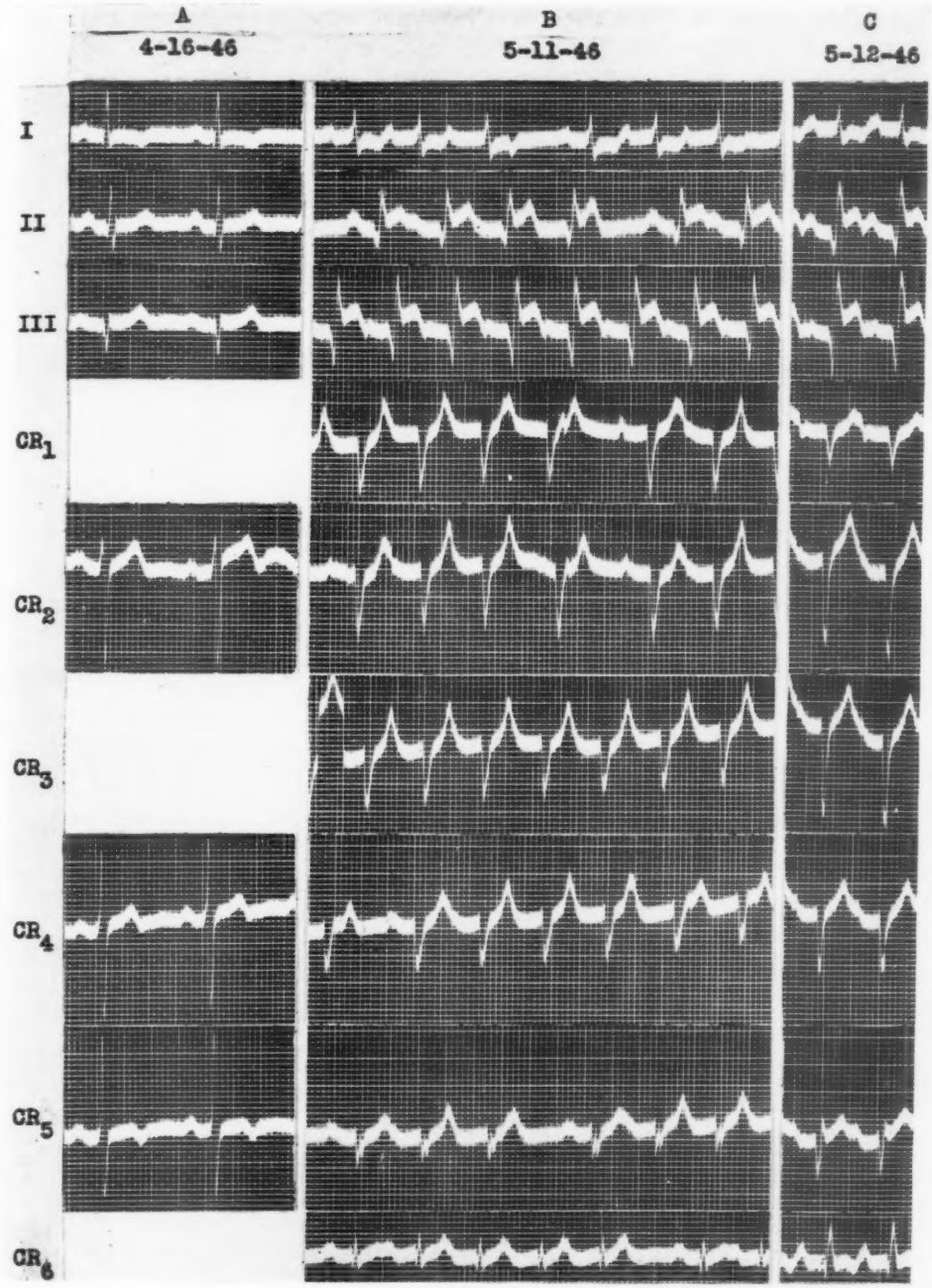

Fig. 2.—Case 2. Recent infarction involving the whole length of the interventricular septum, its entire width in the apical region, and portions adjacent to the septum in the anterior and posterior walls of the left ventricle. Small old anterolateral infarction. *A*, Before the severe coronary attack. Inversion of T in Leads I, CR_4, and CR_5, suggestive of damage in the anterolateral wall. *B* and *C*, Two and three days, respectively, after an attack suggestive of acute coronary obstruction. Signs of acute posterior infarction in the limb leads and of extensive anterior infarction in the chest leads. The leads from the right side of the precordium show more pronounced changes than the leads from the left side.

Summary.—Progressive electrocardiographic changes in the limb leads and in the chest leads from the right side pointed to acute infarction involving the posterior aspect and the anteroseptal walls of the left ventricle. Necropsy revealed a recent infarction which occupied the entire length of the interventricular septum, and extended posteriorly over the apical portion of the left ventricle.

CASE 2.—F. M., a 71-year-old man, suffered from angina of effort for the past seven years, but never had a prolonged attack of chest distress. When he was first examined on April 16, 1946, there were no abnormal cardiac findings on physical examination. An electrocardiogram (Fig. 2, *A*) showed inversion of T in Leads I and CR_5, and a diphasic T wave in CR_4. These changes suggested damage probably in the lateral wall of the left ventricle. On May 9, 1946, the patient suffered a prolonged attack of epigastric pain with nausea and pulmonary edema. After the attack the blood pressure was 80/50 and the heart rate was 138 per minute. The patient died on May 16, 1946.

An electrocardiogram (Fig. 2, *B*), which was taken two days after the attack of pain, showed sinus tachycardia with second degree A-V block. In Leads II and III there were prominent Q waves and marked elevation of the S-T junction. The R deflection was absent in Leads CR_1 and CR_2 and was abnormally small in the other chest leads. In Lead CR_6 a small Q wave preceded an R deflection of low voltage. Tracing *C*, taken a day after *B*, differed only slightly from the previous tracing. In Lead CR_6 the R deflection was larger and was followed by a "coronary T." The changes in the limb leads pointed to acute posterior wall infarction; the changes in the chest leads, which were more pronounced in leads from the right of the precordium, indicated infarction of the anteroseptal area extending rather far toward the left.

Post-mortem examination revealed narrowing of the coronary arteries in multiple spots due to arteriosclerosis. A marked stenosis was present in both the anterior and posterior descending branches at a point about 1 cm. from their origin. The main stem of the right coronary artery was occluded by a fresh thrombus. A large recent infarction extended through the whole length of the interventricular septum and involved its entire width in the apical region. There, the infarction extended over the anterior and posterior surfaces of the right and left ventricles adjoining the septum for a distance of about 2 cm. in the right ventricle and for double that distance in the left ventricle. At the left lateral contour in the apical region a slight bulge, about 2.5 cm. in diameter, was observed; it was formed by scar tissue, the remnant of an older infarction.

Summary.—The electrocardiographic changes suggested acute infarction of the posterior wall and involvement of the anteroseptal wall of the left ventricle. Post-mortem examination showed a recent infarct which occupied the whole length of the interventricular septum and its entire width in the apical region. From the septum the infarction extended over the anterior and posterior walls of both ventricles, occupying an area 2 cm. wide at the right of the septum and an area double that size to the left of the septum. A small, old infarction was present at the anterolateral aspect of the apical region.

CASE 3.—E. P., a 54-year-old woman, was admitted to the hospital in the beginning of 1942 for treatment of diabetes. Her heart was found to be enlarged. The blood pressure was 210/130. An electrocardiogram (Fig. 3, *A*) showed signs suggestive of left ventricular hypertrophy.

During the last two weeks of November, 1942, the patient complained of shortness of breath on exertion. On the evening of Dec. 1, 1942, she experienced pressure in the precordial region for an hour. On the next morning, while walking to the diabetic clinic, she became prostrated and sweated profusely. An electrocardiogram taken on that day (Fig. 3, *B*) showed decrease

of the R deflection in the limb and chest leads. Also, an inverted T with symmetrical limbs was noted in Leads I and CF_5. In Leads CF_3 and CF_4 the S-T junction was elevated and the T wave was semi-inverted. These changes corroborated the impression gained from the history that the patient had suffered a coronary attack with resulting damage to the anterior wall of the heart. An electrocardiogram (Fig. 3, *C*) taken a week after *B*, showed but slight changes. In Lead CF_3 the R wave had become very small and inversion of T was less pronounced; there was sharp inversion of T in Leads CF_4 and CF_5.

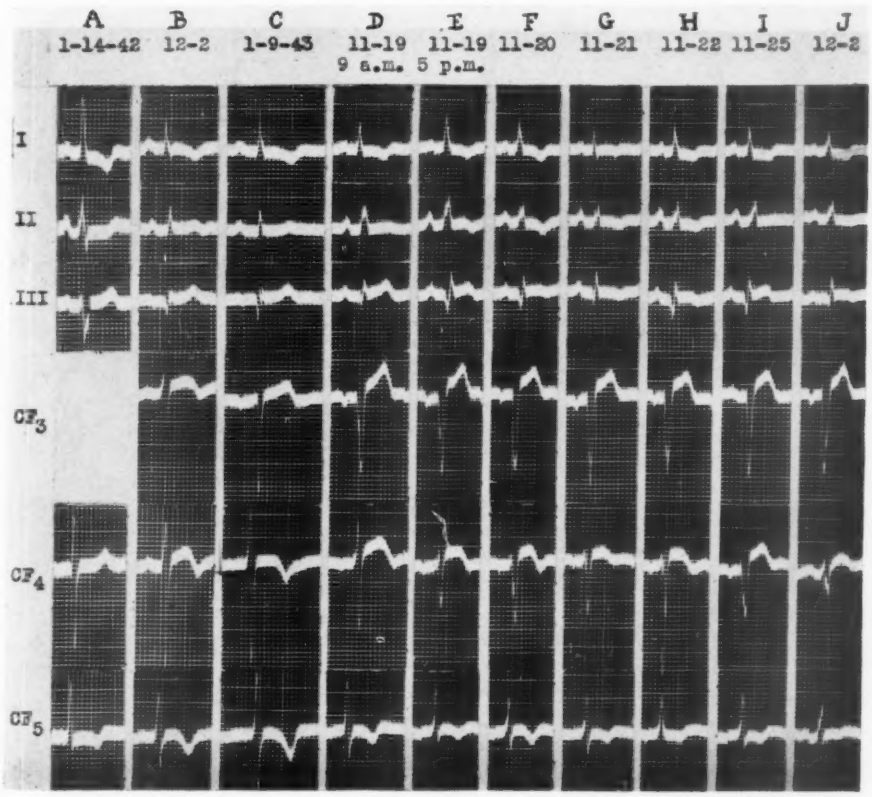

Fig. 3.—Case 3. Recent infarction of the lower part of the interventricular septum, merging with small areas of infarction in the anterior and posterior walls of the left ventricle. *A*, Before the severe coronary attack. Signs suggestive of left ventricular hypertrophy. *B* and *C*, After a minor coronary attack in November, 1942. Signs of damage in the anterior wall. *D* through *J*, Following a severe coronary attack on Nov. 19, 1943. Signs of posterior and anteroseptal infarction with little tendency toward progressive changes.

On the morning of Nov. 19, 1943, the patient again suffered an attack of severe substernal tightening and was admitted to the hospital. She was in shock and presented signs of pulmonary congestion. An electrocardiogram taken on that day (Fig. 3, *D*) showed a small Q wave in Lead III and decrease of the amplitude of R in the chest leads. The S-T junction was elevated in Leads III, CF_3, and CF_4. T_2 was dome-shaped; the amplitude of T_3 had increased. There was also an increase in the voltage of T in CR_3 and CR_4. The next tracing (Fig. 3, *E*), which was taken eight hours after *D*, showed further changes: Q_3 was broader and deeper; there was terminal inversion of T_2 and T_3; in Lead CF_4 the amplitude of R had further decreased, and there was abnormal elevation of the S-T junction, coupled with inversion of T.

The patient developed low-grade fever and leucocytosis. The signs of pulmonary congestion persisted. Serial electrocardiograms taken on November 20, 21, 22, 25, and on December 2 (Fig. 3, *F-J*) showed little tendency to change. In Leads III, CF_3, and CF_4, the S-T junction remained elevated and there was little progress toward complete inversion of T. Death occurred on Dec. 8, 1943.

Post-morten examination revealed marked arteriosclerosis of the coronary arteries. The lumina of the posterior descending and right marginal branches were reduced to pin-point size. The distal ramifications of the anterior descending branch were almost completely obliterated. An area of recent infarction, measuring 2.0×1.5 cm., was found at the base of the posterior wall. It merged with a recent infarction of the interventricular septum, which extended through the lower half of the septum toward the anterior aspect of the heart and merged there with a recent infarction in the apical area, which measured 2.5×1.0 centimeters.

Summary.—A minor coronary attack in November, 1942, had resulted in damage to the anterior wall, as indicated by the electrocardiogram. Following another attack in November, 1943, the electrocardiogram showed signs of infarction in Leads II and III and in leads from the right side of the precordium. Post-mortem examination revealed a recent infarct which occupied the lower part of the interventricular septum and merged with small areas of infarction, apparently of the same age, in the anterior and posterior walls of the left ventricle.

CASE 4.—S. E., a 55-year-old woman, had diabetes and hypertension for many years. On Jan. 11, 1942, she was seized with crushing pain in the precordial region and left shoulder. The attack lasted for several hours. It was followed by fever and increase of the white blood count and sedimentation rate.

An electrocardiogram was available which had been taken in 1939, two and one-half years prior to the pain attack (Fig. 4, *A*). It showed signs suggestive of left ventricular hypertrophy. A tracing taken two days after the attack (Fig. 4, *B*) showed significant changes. In Lead II there was a prominent Q deflection; the S-T junction was elevated; the S-T segment upward-convex; and the T wave semi-inverted. In Lead IV F the R deflection had disappeared, the S-T segment was elevated, and the T wave was sharply inverted. Another electrocardiogram, taken eight days after the attack (Fig. 4, *C*) showed even more pronounced elevation of S-T in Leads II and III, and straightening of the S-T segment in Lead III. In the following two tracings (*D* and *E*) progressive inversion of T in Leads II and IV F was noted.

The patient suffered two more attacks of prolonged precordial pain in April, 1942. However, the electrocardiogram (Fig. 4, *F*) showed only regressive changes of T. Death occurred on April 26, 1942.

Post-mortem examination revealed diffuse arteriosclerosis of the coronary arteries. The anterior descending branch was occluded by a recent thrombus about 2 cm. from its origin. Below the point of recent occlusion, there was almost complete obliteration of the lumen due to the arteriosclerotic process. The left circumflex and the posterior descending branches were moderately narrowed. The weight of the heart was 520 grams. The lower half of the left ventricle was thinned out and showed slight aneurysmal dilatation. The myocardium of the entire lower half of the interventricular septum was replaced by fibrous tissue which merged with scar tissue in the anterior wall of the left ventricle. In addition there was a recent infarction which involved the lower part of the posterior and lateral walls of the left ventricle.

Summary.—There had been two coronary attacks; one three and one-half months and the other two and one-half weeks prior to death. After the first attack, the electrocardiogram showed a Q_3-T_3 pattern and significant changes in Lead IV F, suggesting acute posterior and anterior infarctions. Although

only one chest lead was available, absence of significant changes in Lead I suggested an anteroseptal rather than an anterolateral site of infarction. These electrocardiographic changes obviously corresponded to the older, healed infarction which was revealed by necropsy. It occupied the entire lower half of the interventricular septum and an adjacent portion of the anterior wall of the left ventricle.

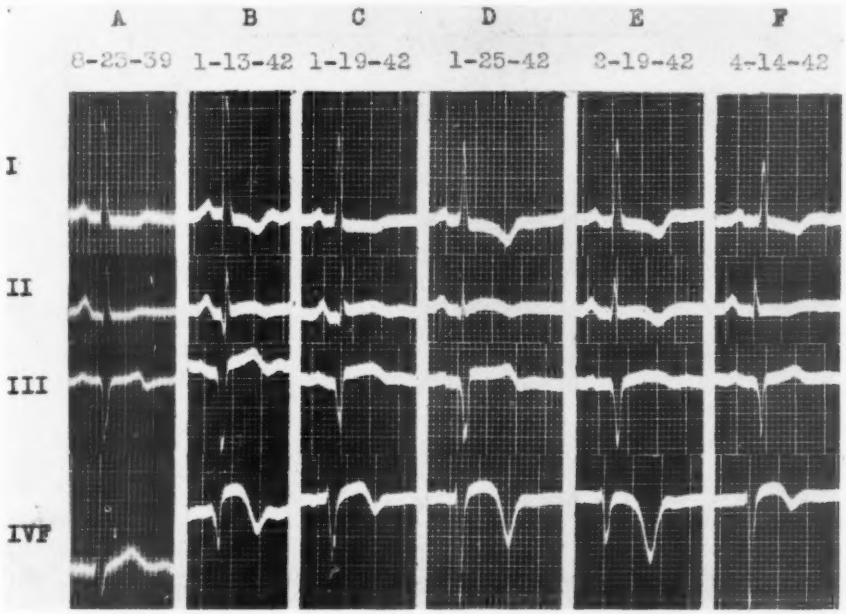

Fig. 4.—Case 4. Healed infarction occupying the lower half of the interventricular septum and an adjacent portion of the anterior wall of the left ventricle. Recent infarction involving the lower part of the posterior and lateral walls of the left ventricle. *A*, Before the severe coronary attack. Signs suggestive of left ventricular hypertrophy. *B* through *E*, Two days after a severe coronary attack. Signs of posterior and anterior infarction; progressive changes. *F*, After two new attacks of prolonged chest pain; no significant changes.

Case 5.—E. S., a 69-year-old man, complained of substernal tightness on exertion for the past several years. Three weeks prior to admission to the hospital, the patient suffered an attack of "gas pain across the back." This was followed, five days before admission, by a more severe attack of chest pain which was relieved by morphine. The patient was admitted to the hospital on Jan. 17, 1939. After the second attack, the blood pressure dropped to 86/62. The heart sounds were distant and a pericardial friction rub was heard. Low-grade fever and leucocytosis developed. Death occurred nine days after the second attack.

An electrocardiogram (Fig. 5) was taken on Jan. 17, 1939, five days after the second attack of severe pain. It showed a Q_3-T_3 pattern and changes suggestive of anteroseptal infarction in Leads CF_2 and CF_4.

Post-mortem examination revealed stenosis of the coronary arteries due to arteriosclerosis which was most marked in the anterior descending branch. There was a huge recent infarction which involved almost the entire lower two-thirds of the interventricular septum and an adjoining area of the anterior wall of the left ventricle. Posteriorly, the infarction extended for about 0.5 cm. to the right of the septum.

Summary.—The electrocardiogram showed changes significant of posterior and anteroseptal infarction. Post-mortem study revealed a huge recent infarct that occupied nearly the entire lower two-thirds of the interventricular septum and an adjoining area of the anterior wall of the left ventricle; posteriorly, a very narrow strip to the right of the septum was involved.

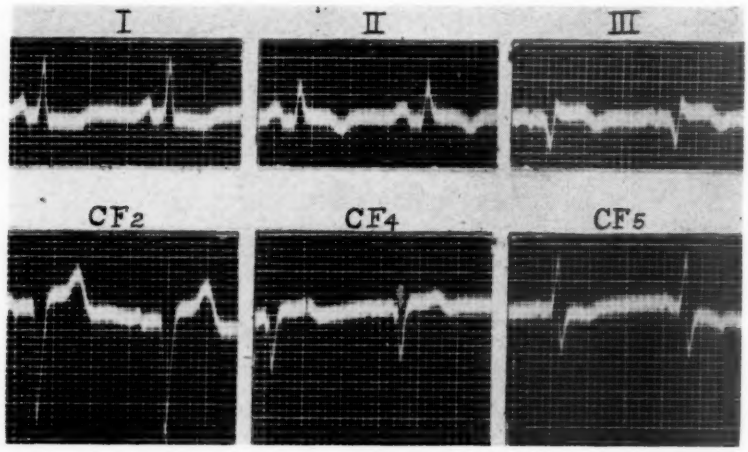

Fig. 5.—Case 5. Recent infarction occupying almost the entire lower two-thirds of the interventricular septum and an adjoining area of the anterior wall of the left ventricle, extending posteriorly for 0.5 cm. to the right of the septum. Five days after the coronary attack, the electrocardiogram shows signs of posterior and anteroseptal infarction.

COMMENT

All cases in this report showed electrocardiographic signs of both posterior and anterior wall infarction. Where multiple chest leads were available (Cases 1, 2, 3, and 5), an anteroseptal site of infarction was indicated by significant changes in leads from the right side of the precordium as far as Position C_4. In Case 4 only one chest lead (IV F) was taken and it showed signs of anterior infarction. Since significant changes were absent in Lead I, which usually reflects changes of potential in the left lateral wall, an anteroseptal rather than a lateral site of the infarction was suggested. Progressive changes in limb and chest leads were observed in Cases 1, 3, and 4; this indicated that posterior and anterior infarctions were of recent origin and of approximately the same age.

In all cases, infarction of the interventricular septum was the outstanding post-mortem finding. In three instances the infarction was very extensive, occupying either the whole length of the septum (Cases 1 and 2) or almost the entire lower two-thirds of the septum (Case 5). In two cases (Cases 3 and 4) the lower half of the interventricular septum was the site of infarction. In all instances, the infarction extended from the anterior to the posterior aspect of the heart, encroaching upon a portion of either the anterior (Case 4) or posterior wall (Case 1), or both (Cases 2, 3, and 5).

In the case published by Wilson and associates,[2] it was not revealed how large a portion of the septum was involved. In a drawing of a cross section of

the heart, it was indicated that the infarction extended from the anterior wall through the septum to the posterior wall of the left ventricle. Wolferth and Wood[3] reported cases of "acute cardiac infarction involving anterior and posterior surfaces of the left ventricle." Signs of acute infarction were present in Leads II and III and in chest leads taken from the apical area. Three of their cases were necropsied. In one (Case 1) the autopsy report stated that "the interventricular septum was almost completely infarcted" in addition to portions of the anterior and posterior walls of the left ventricle. In their Case 11, an infarction involved the lower half of the interventricular septum and parts of the anterior and posterior walls of the left ventricle. In Case 2 an aneurysm was found at the posterior wall which merged with fibrotic changes in the anterior apical portion of the left ventricle. No mention was made of involvement of the interventricular septum. Clapper, Myers, and Oren[6] reported on cases of myocardial infarction involving the anterior and posterior aspects of the apex of the left ventricle. The electrocardiogram showed a Q_3-T_3 pattern and significant changes in the chest leads from Positions C_3 and C_4.

References to septal infarction are scarce in the literature. In our search for pertinent cases, we examined reports on rupture of the interventricular septum secondary to myocardial infarction. Unfortunately, the majority of the considerable number of case reports includes either no electrocardiogram or only the three standard leads. We found only two cases in which, in addition to the standard leads, Lead IV F was available.[4,5] Both cases showed the Q_3-T_3 pattern and significant changes in Lead IV F. In one case[4] a ventricular aneurysm was present and the post-mortem report stated that "the aneurysm, in addition to involving the apical third of the interventricular septum, extended upward from the apex on to the anterior left ventricular wall for a distance of 4.5 cm., and upward from the apex on the posterior left ventricular wall for a distance of 1.5 cm." In the other case of ruptured interventricular septum,[5] the post-mortem examination revealed an "infarction of the lower half of the interventricular septum and the immediately adjacent anterior apical portions of the left ventricle."

The findings in the literature are in accord with our own observations concerning the significance of the Q_3-T_3 pattern which is combined with signs of anterior (anteroseptal) infarction.

It should be mentioned that Wilson has pointed out that infarction of the interventricular septum is indicated in cases of left bundle branch block by the presence of significant Q waves in the chest leads. We were able to confirm this view on the basis of post-mortem findings in two cases which showed these electrocardiographic features.

SUMMARY

Five cases are reported which presented in the limb leads signs of posterior wall infarction and, simultaneously, in the precordial leads, signs of anteroseptal infarction. Post-mortem examination showed in all cases infarction of the interventricular septum that extended from the anterior to the posterior aspect

of the heart and involved variable portions of the anterior or posterior wall adjacent to the septum. Similar cases are quoted from the literature.

It is suggested that extensive infarction of the interventricular septum, reaching from the anterior to the posterior aspect of the heart, be considered when the electrocardiogram shows a Q_3-T_3 pattern and diagnostic signs of infarction in leads from the right side of the precordium, and when the changes in the limb and chest leads indicate the same stage of acute or subacute infarction. A similar electrocardiographic pattern sometimes is observed when infarction in the apical region extends from the anterior to the posterior aspect of the heart.

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MYOCARDITIS

A Classification of 1402 Cases

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THE autopsy material submitted to the Army Institute of Pathology during the recent war contained an unusually large number of cases of myocarditis. In view of current interest in this subject aroused by the reports of transitory electrocardiographic alterations in a number of different diseases, a review of this wealth of material was considered important in determining an anatomic background for such changes. A total of 1,402 cases of myocarditis verified by pathologic examination was available for review.

The clinical diagnosis "myocarditis" fell into disrepute in the early part of this century following a period in which it had been used indiscriminately to designate any cardiac disorder not accompanied by an organic murmur. Naturally, many instances of hypertensive and arteriosclerotic heart disease were misdiagnosed. It became almost axiomatic, therefore, to state that myocarditis for all practical purposes did not exist, except as a result of rheumatic fever and diphtheria. Although such a view undoubtedly has had a beneficial effect on accuracy of diagnosis and augmented knowledge of heart diseases, it would appear that, since hypertensive and arteriosclerotic heart disease are so thoroughly recognized, this working rule has served its clinical usefulness and had better be discarded. Further perpetuation of the idea it embodies will only serve to hinder progress. To have followed such a rule would have prevented recognition of myocarditis in 75 per cent of the cases making up the material on which this report is based; and as a matter of fact, the records show the correct diagnosis was rarely made.

In recent years considerable interest has been aroused by the publication of a number of case reports of Fiedler's (idiopathic, or isolated) myocarditis. The clinical records not infrequently refer to an acute febrile illness shortly antecedent to, or coincident with, the onset of the cardiac disorder. To assay the significance of such acute illnesses in relation to cardiac symptoms, it was necessary to review not only a large number of cases of myocarditis, but also to ascertain the incidence of carditis in various acute diseases. Saphir[1] made such a review in 1941, reporting a series of 240 cases of myocarditis encountered in 5,626 consecutive au-

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topsies. One hundred eighty-six of the reported cases were nonrheumatic, and in a distressing proportion the myocarditis had gone unrecognized by the clinicians who had studied the cases in life. Similar observations can be made on the 1,402 cases accumulated at the Army Institute of Pathology. There were only 130 cases of rheumatic carditis, so that the heart condition in more than 90 per cent of the series was nonrheumatic. Clinically, myocardial involvement had not been suspected in the majority of these. The proportion of missed diagnoses becomes still more impressive if the diphtheria cases, constituting approximately 10 per cent of the total, are excluded; but for that matter, the cardiac complication was recognized in only one-third of them.

The diagnostic failure can not be attributed to an absence of signs or symptoms. The clinical records frequently mention cyanosis, dyspnea, and orthopnea. A significant degree of hypotension was often observed, and with it a weak, feeble, or thready pulse. Often the recorded pulse rate and temperature showed a loss of the normal ratio. Sometimes chest pain, characterized by substernal oppression or discomfort, was observed. Electrocardiograms, in the majority of instances in which they were taken, disclosed evidence of myocardial damage. Manifestations of congestive heart failure, which occurred in an appreciable number of cases, included distended neck veins, serous effusions, swollen tender liver, and dependent edema. Unexpected deaths were numerous, and in the small group of patients who survived for periods ranging from one to six months, embolic phenomena were observed.

The importance of overcoming the prevailing prejudice against the diagnosis of myocarditis is well demonstrated in a review of the available records of scrub typhus fever. The clinical recognition of myocarditis in this disease became more frequent as the initially inexperienced physicians became aware of the remarkably high incidence of carditis encountered in fatal cases. Needless to say, there had been no change in the clinical manifestations observed but merely an increased awareness of them and a more accurate evaluation of their significance.

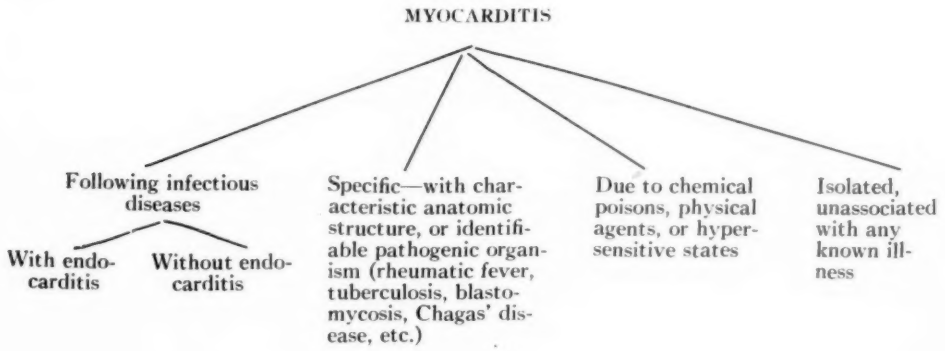
Table I is included to indicate the wide variety of diseases and conditions that were found associated with the myocarditides encountered in this series. The known etiological agents include: toxic substances (diphtheria); physical or chemical agents (heat stroke and carbon monoxide poisoning); various specific virus, rickettsial, spirochetal, and fungus diseases; less specific infectious processes; and various metabolic states such as inanition and hypersensitivity. It would be a mistake to conclude that such a grouping is sharp and distinctive. For example, it is impossible to evaluate properly the effects of absorbed toxins, bacterial infections, and treatment in the myocarditis associated with burns, or of secondary bacterial infections so frequently complicating primary virus diseases. Nor are these the only conditions in which other infectious processes interfere with analysis of the cardiopathic effect; only six of the thirty-three cases of starvation associated with myocardial inflammation could not be related to a coexistent infectious process. In other diseases, such as infectious mononucleosis, acute infectious polyneuritis (Guillain-Barré syndrome), and Boeck's

TABLE I. DISEASES ASSOCIATED WITH MYOCARDITIS*

	COLUMN 1	COLUMN 2		COLUMN 1	COLUMN 2
Rickettsial diseases			Septicemia		
Scrub typhus	227	227	Streptococcus	11	23
Epidemic typhus	23	48	Staphylococcus	34	107
Rocky Mountain spotted fever	9	19	Pneumococcus	9	18
Diphtheria	144	221	Other acute bacteremias	15	Unknown
Subacute bacterial endocarditis	208	208			
Rheumatic heart disease	130	130	Acute glomerulonephritis	14	160
Meningococcemia	111	256	Acute tonsillitis	12	Unknown
Scarlet fever	24	44	Acute nasopharyngitis	41	Unknown
			Cellulitis, lymphangitis, and wound infections	13	Unknown
Weil's disease	7	8			
Relapsing fever	6	11	Tularemia	1	16
Syphilis (gummatous)	2	66	Brucellosis	2	4
			Miscellaneous (postinfectious)	13	Unknown
Chagas' disease	1	1			
Schistosomiasis	5	41	Exfoliative dermatitis	7	44
Malaria	5	135	Arsenical reaction	1	18
Trichinosis	2	2	Sulfonamide hypersensitivity	105	Unknown
Acute encephalitis	13	144	Disease unknown (so-called "idiopathic")	43	
Poliomyelitis	13	94			
Infectious mononucleosis	6	9	Starvation	33	50
Measles					
Guillain-Barré syndrome	3	30	Heat stroke		
Mumps	1	8	Surviving less than 24 hours	16	45
Epidemic hepatitis	1	400	Surviving more than 24 hours	13	26
Smallpox	1	9	Carbon monoxide poisoning	1	30
Virus pneumonia	32	222	(limited to patients who survived for an appreciable interval after the lethal exposure)		
Tuberculosis	9	581			
Boeck's sarcoid	3	12	Emetine	1	70
Coccidioidomycosis	11	48	Burns	11	45
Blastomycosis	2	5			
Actinomycosis	1	9			
Torulosis	1	6			
			Total	1,402	

*The figures in the first column represent the number of times myocarditis was encountered. Wherever possible the number of cases of each disease, screened to ascertain the first figure, is given in column two. The ratio of the two thus provides a crude index of the frequency of myocarditis in each disease.

sarcoid, the current limitations of medical knowledge prevent proper cataloguing. A useful inclusive working classification, although one not free from the criticism of overlapping, is that proposed by Saphir.



A number of studies are contemplated to analyze the material at the Army Institute of Pathology, and will include the myocarditides associated with sulfonamide administration, acute infections of the upper respiratory tract, acute glomerulonephritis, acute meningococcemia, scarlet fever, diphtheria, spirochetal diseases, fungus diseases, certain parasitic diseases, rickettsial diseases, virus diseases, tuberculosis, Boeck's sarcoid, exfoliative dermatitis and septicemias, including subacute bacterial endocarditis.

It is perhaps worthy of note for its negative value only, that myocarditis was not encountered among eighty cases of typhoid fever, nor in thirty cases of bacillary dysentery. The former disease, particularly, has been classically associated with the production of Zenker's hyaline degeneration of skeletal muscle.

Although some of these myocarditides may be considered of academic rather than clinical interest, it is axiomatic that sound therapy can be based only on an accurate appraisal of the pathologic alterations. For example, myocarditis occurring with septicemia and subacute bacterial endocarditis, an academic problem prior to the adoption of sulfonamides and penicillin, is responsible for many of the fatalities in "bacteriologically cured" or arrested cases treated with these newer therapeutic agents.

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MYOCARDITIS ASSOCIATED WITH ACUTE NASOPHARYNGITIS AND ACUTE TONSILLITIS

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NONRHEUMATIC myocarditis occurring in the course of, or following acute infections of, the upper respiratory tract is a relatively unexplored subject. Rantz, Boisvert, and Spink,[1] who were associated with the Commission on Hemolytic Streptococcal Infections during World War II, set the incidence of this complication at 10.8 per cent. Their convincing epidemiologic and clinical studies did not include anatomic data. The series of eleven nonfatal cases of myocarditis following various infectious diseases reported by Candel and Wheelock[2] included one in which peritonsillar abscess was present. They also described one fatal case in which myocarditis was observed at postmortem examination after acute tonsillitis. Scherf[3] reported five nonfatal cases in which myocarditis followed acute tonsillitis, and stated that in his experience this complication occurred in 10 to 15 per cent of such cases. Substantial pathologic verification would be needed, however, before such high incidence could receive more than probational acceptance from the wary clinician (Saphir[4]).

In a study of the pertinent material available at the Army Institute of Pathology, thirty-five instances of nonrheumatic myocarditis were encountered in association with upper respiratory infections: acute tonsillitis in twelve† (Cases 1 through 12); and acute nasopharyngitis in twenty-three (Cases 13 through 35). In all cases the diagnosis of pharyngeal or tonsillar infection had been made clinically. Streptococci were cultured from the throat in twelve and from the heart's blood, post mortem, in three; grouping and subtyping had not been done. Septicemia was not considered of etiological moment since significant visceral alterations were absent in all thirty-five, and negative blood cultures were obtained in thirteen. *Corynebacterium diphtheriae* was absent from the culture material and diphtheria had been excluded clinically in each instance. The patients, with one exception (Case 35), were men; most of them were between 20 and 30 years of age, the youngest being 18 years and the oldest 43 years of age. More detailed information is available in Table I and in the appended clinical summaries.

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†One of these twelve patients died of acute heart failure on the sixth day following tonsillectomy (Case 4).

TABLE I. CLINICAL AND ANATOMIC FEATURES OF MYOCARDITIS IN THIRTY-FIVE CASES OF ACUTE TONSILLITIS AND ACUTE NASOPHARYNGITIS

CASE NO.*	DURATION IN DAYS	CLINICAL MANIFESTATIONS OF HEART DISEASE PRESENT	STREPTOCOCCI IN THROAT CULTURE	BLOOD CULTURE	SULFA MEDICATION	BLOOD PRESSURE	TEMPERATURE/PULSE DISPROPORTION	BRONCHOPNEUMONIA	SEROUS EFFUSION	OTHER COMPLICATIONS
1	4	0	–	–	+	130/70	101°–80	0	–	–
2	4	+	+	0	0	104/60	98.8–110	0	–	–
3	5	0	+	–	+	–	–	0	–	–
4	5	+	–	0	+	130/80	103.2–88	0	–	–
5	8	+	+	–	+	–	102–130	+	–	Pericarditis
6	10	+	–	0	+	85/70	–	0	–	Anuria
7	13	+	–	0	+	90/60	–	0	–	Peritonsillar abscess
8	14	+	–	–	+	85/60	–	0	+	–
9	14	0	–	0	0	85/55	–	0	+	–
10	14	+	+	–	+	–	–	0	–	–
11	17	+	–	–	+	–	–	0	–	–
12	17	?	–	–	+	–	–	+	+	–
13	3	+	+	–	0	–	105 – 110	+	+	–
14	3	0	–	0	+	–	104.3–108	0	+	–
15	5	+	+	0	+	–	0	+	+	–
16	5	0	+	–	+	110/68	–	I†	–	–
17	5	0	–	0	0	–	99.4–104	0	–	–
18	6	0	–	–	+	115/70	–	+	+	–
19	6	+	–	–	+	–	–	0	+	Anuria
20	7	0	+	0	0	–	101 – 86	0	+	–
21	7	0	+	+	+	–	–	+	+	–
22	7	+	–	0	+	94/64	105.2–108	0	+	–
23	8	+	+	–	+	–	102 – 140	I†	+	–
24	8	+	–	–	+	130/76	–	+	+	Pulmonary infarction
25	8	+	–	0	0	120/80	98.6–168	+	+	–
26	9	+	–	0	0	84/70	–	I†	+	–
27	11	?	+	+	+	–	–	+	+	–
28	14	+	–	–	+	–	–	+	+	–
29	16	0	–	–	+	122/74	–	0	–	–
30	17	+	–	–	+	98/42	101.4–130	0	–	–
31	19	+	–	–	+	90/50	105.4–158	0	–	Urachal sinus
32	23	0	+	+	+	118/60	–	+	–	–
33	24	+	–	–	+	106/70	103 – 90	+	–	Pericarditis
34	33	0	–	–	0	–	101.2– 78	0	–	–
35	38	+	–	0	0	94/82	98.6–108	0	+	Visceral infarcts

*Cases 1 through 12 are acute tonsillitis, 13 through 35 are acute nasopharyngeal infections.
† Signifies an interstitial type of bronchopneumonia.

CLINICAL OBSERVATIONS

Elevation of temperature noted in thirty-three patients ranged between 99° and 104.4°F., averaging about 102°Fahrenheit. The pulse rate varied from 60 to 168 per minute. In fourteen the pulse rates and temperatures did not show proportionate variations; the pulse rate was disproportionately fast in six and disproportionately slow in eight. Cyanosis was noted in twelve patients, frequently in association with dyspnea which was observed in sixteen. Cheyne-Stokes respiration was present in two patients. Oppressive substernal pain was encountered in six, in every instance associated with dyspnea.

Electrocardiographic studies in five cases showed evidence of "myocardial damage" in three and disturbances in rhythm in two.

Hypotension occurred as a prominent clinical feature in five of twelve patients with nasopharyngitis in whom arterial blood pressures were recorded. There was low arterial tension in four of the seven patients with tonsillitis whose blood pressure readings were available. The values of these readings ranged from 98/42 to 85/55; there were five patients with systolic pressures of from 90 to 100 and four with pressures of from 80 to 90. A weak thready pulse, presumptive evidence of low blood tension, was observed in seven patients.

Twenty-six patients received sulfonamides; many were also given penicillin. Intravenous fluids were frequently administered, especially in the terminal phase of the illness. Azotemia as a result of urinary suppression developed in two of the patients who had received sulfonamides (Cases 6 and 19); their blood nonprotein nitrogen estimations were 85 and 210 mg. per cent, respectively.

The duration of hospitalization among the patients with nasopharyngitis averaged seven days, although five died within twenty-four hours (after illnesses which had begun from three to eight days before) and two survived for twenty-four days. Length of hospitalization among the patients with tonsillitis averaged eight and one-half days. The significant clinical manifestations of cardiac dysfunction are summarized in Table II; more detailed information may be obtained by referring to the appropriate case number in Table I and to the appended clinical summaries.

POST-MORTEM OBSERVATIONS

The cause of death was determined as cardiac failure in all cases. There were fifteen unexpected deaths, and in the remaining cases the pathologic findings included passive hyperemia of the viscera in all, pulmonary edema in most, and serous effusions in seventeen (ten of these were either extrathoracic or were unassociated with a pneumonic process).

In addition to cardiac changes, certain other abnormalities were noted at autopsy. Among the twenty-three patients with nasopharyngitis, ten had bronchopneumonia and three had interstitial pneumonia. Streptococci were cultured from the lungs of five and two of these, respectively. Thrombi were found in the left ventricle in one case in which there were also visceral infarcts and gangrene of the right leg. Pulmonary infarcts of unspecified origin were observed in another.

† Signifies an interstitial type of bronchopneumonia.

TABLE II. CLINICAL MANIFESTATIONS OF HEART DISEASE IN TWELVE CASES OF ACUTE TONSILLITIS AND TWENTY-THREE CASES OF ACUTE NASOPHARYNGITIS

	OCCURRED IN CASES	TOTAL NO. OF CASES
Cyanosis*	4, 5, 13, 16, 20, 23, 25, 26, 27, 29, 30, 35	12
Dyspnea* and/or orthopnea	4, 5, 15, 16, 20, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 35	16
Cheyne-Stokes respiration	8, 21	2
Cardiac arrhythmia or irregularity	4, 5, 6, 10, 11, 13, 15, 22, 25, 26, 31	11
Disproportions of temperature and pulse	1, 2, 4, 5, 13, 14, 17, 20, 22, 23, 25, 30, 31, 33	14
Hypotension and/or weak thready pulse	6, 7, 8, 9, 11, 22, 25, 26, 30, 31, 35	11
Anginal pain	6, 9, 22, 25, 34, 35	6
Abnormal electrocardiogram	6, 10, 26, 33, 35	5
Unexpected death	1, 3, 9, 15, 16, 17, 18, 19, 20, 21, 22, 25, 29, 31, 34	15
Enlarged heart (x-ray)	19, 25, 30, 33, 35	5
Enlarged and tender liver	8, 25, 35	3
Pulmonary edema	14, 19, 23, 27, 32	5
Dependent edema	28, 35	2
Pulsus paradoxus	25	1

***A pneumonic process occurred in seven of the cases presenting cyanosis and in ten of the cases with dyspnea. Case numbers 1 through 12 represent acute tonsillar infection, numbers 13 through 35 refer to acute nasopharyngitis. In each case, reference to the appropriately numbered clinical summary will provide more detailed information.**

Among the twelve cases of tonsillitis, bronchopneumonia and pericarditis occurred in one, bronchopneumonia with abscess formation in another, and peritonsillar abscess in a third. The parenchymatous organs in all 35 cases were the seat of varying degrees of cloudy swelling. There was moderate renal tubular damage and interstitial cellular infiltration in the two cases in which azotemia developed; sulfa crystals were identified in one of these. (See Table I and clinical summaries.)

Cardiac Findings.—At autopsy all but six of the hearts were found to be dilated; frequently they were increased in weight. Figures on the weights of organs were available in twenty-eight cases; the heart weighed 400 grams or more in thirteen (in three of these, 400 grams; between 400 and 499 grams in six; and between 500 and 560 grams in four). In the remaining cases one heart was regarded as "enlarged;" one, in a woman of average size, weighed 350 grams; two hearts were considered to be normal; three weighed less than 300 grams; and ten, between 300 and 400 grams. In the absence of hypertension or other possible causes for cardiac hypertrophy, the inflammatory process within the myocardium must have been largely responsible for the augmented weights.

Grossly, the hearts were usually described as soft, flabby, and friable. There was pallor of the myocardium which was gray or gray-streaked, or mottled with red or yellow, or both. Petechial hemorrhages were found subepicardially seven times and diffusely scattered throughout the myocardium three times. Mural ventricular thrombi were encountered in one case. Five of the hearts were regarded as grossly normal.

Histologically, the changes in the myocardium were striking. The lesions varied from circumscribed focal areas of inflammation, principally involving the interstitial tissues (Fig. 1), to areas of diffuse inflammatory infiltration associated with necrosis of muscle fibers (Fig. 2). Gradations from obviously very recent inflammation to definitely healing and organizing lesions were observed. The inflammatory process was patchy in distribution and there appeared to be no special region of the myocardium for which it had a predilection. When the heart was severely involved the intensity of the process frequently varied from one section to another. In instances of less intense involvement, it was not uncommon to find areas of the heart muscle in which inflammatory changes were minimal or even absent.

The inflammatory cellular response was predominately and characteristically mononuclear (Figs. 3 and 4). The proportion of each cell type encountered was not uniform and varied from one area to another. In the most cellular zones lymphocytes outnumbered the other elements, which included endothelial leucocytes and Aschoff cells,* mononuclear cells larger than lymphocytes with densely stained nuclei, and polymorphonuclear leucocytes. Occasionally, the last cell named made up as much as one-third of those present, but abscesses were not encountered. Polymorphonuclear leucocytes were less numerous in areas of less intense inflammation, and endothelial cells and Aschoff cells predominated in the areas where inflammation was least. These endothelial and Aschoff cells frequently formed small accumulations about a few intensely acidophilic, homogeneous muscle fibers, or somewhat more diffusely infiltrated the interstitial tissues, especially subendocardially about the orifices of the Thebesian vessels. The focal cellular accumulations around a few necrotic muscle fibers appeared to represent a very early and rapid morphologic change which we have designated as an "explosive lesion" (Figs. 5 and 6). Plasma cells and eosinophils were found in varying numbers. In older lesions fibroblasts were observed. Mast cells were present, as they are normally, but did not appear to participate to any extent in the inflammatory reaction. Bacteria were absent from all sections examined. Accompanying the inflammatory cells there was exudation of variable quantities of protein-rich fluid into the interstitial tissues.

The lesion involved both the scanty stroma within the muscle fasciculi and the more abundant stroma accompanying the blood vessels in the interfasicular septa. On this basis three histologic types of myocarditis could be distinguished. The first, which we have designated the *diffuse* variety, affected both

*Characterized by an abundant, faintly basophilic cytoplasm, a lightly stained oval nucleus, a thin sharp nuclear membrane, and a characteristic arrangement of the chromatin in the form of a central bar or node from which web-like processes extend toward the periphery; frequently called the "myocyte" following Anitschkow's original interpretation.

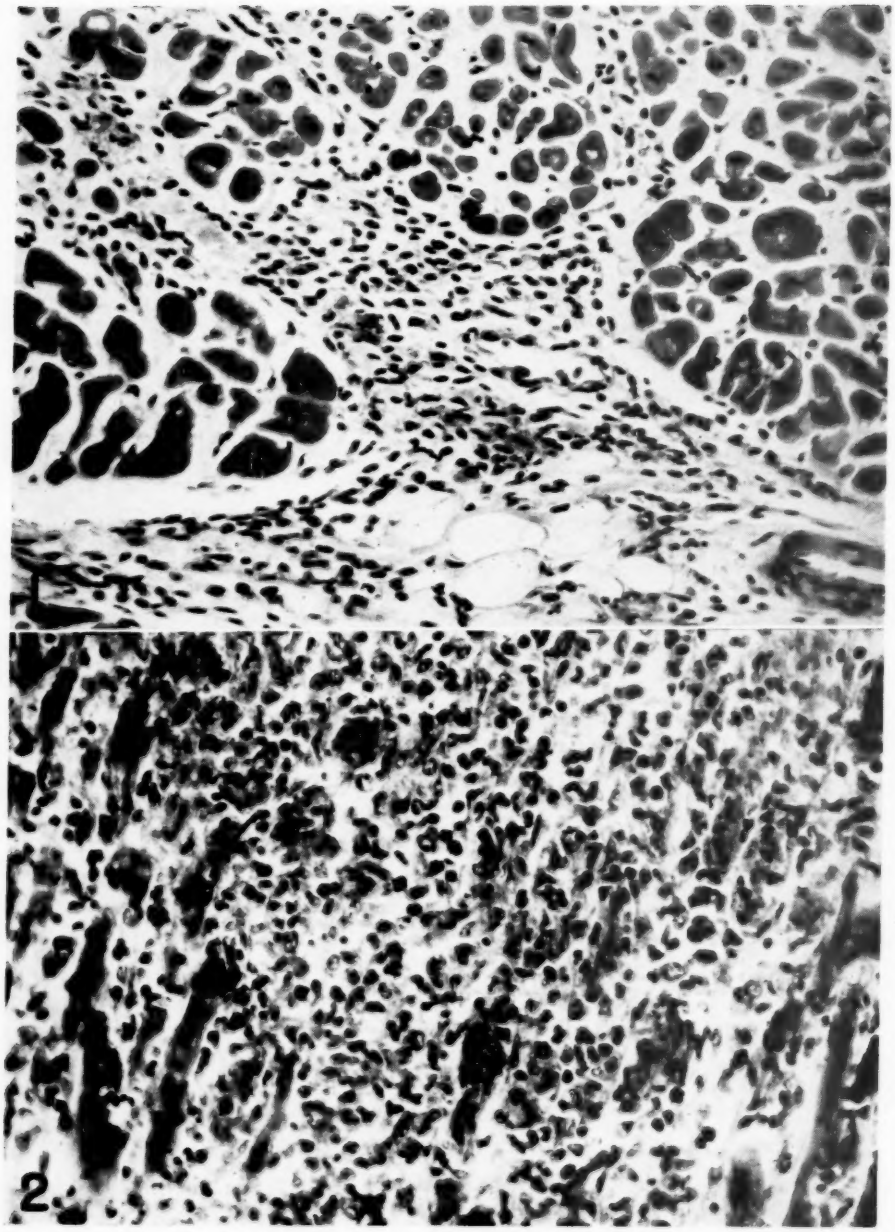

Fig. 1.—Case 3, AIP Accession 106073. Interstitial type of myocarditis. Note the predominantly mononuclear leucocytic infiltration of the stromal septa separating the muscle fasciculi. × 275. Neg. 95854.

Fig. 2.—Case 34, AIP Accession 103357. Diffuse type of myocarditis. There has been rather extensive degeneration of the muscle fibers which are replaced by an intense, largely mononuclear, inflammatory infiltrate. Fibroblasts may also be identified in the lesion. × 310. Neg. 95857.

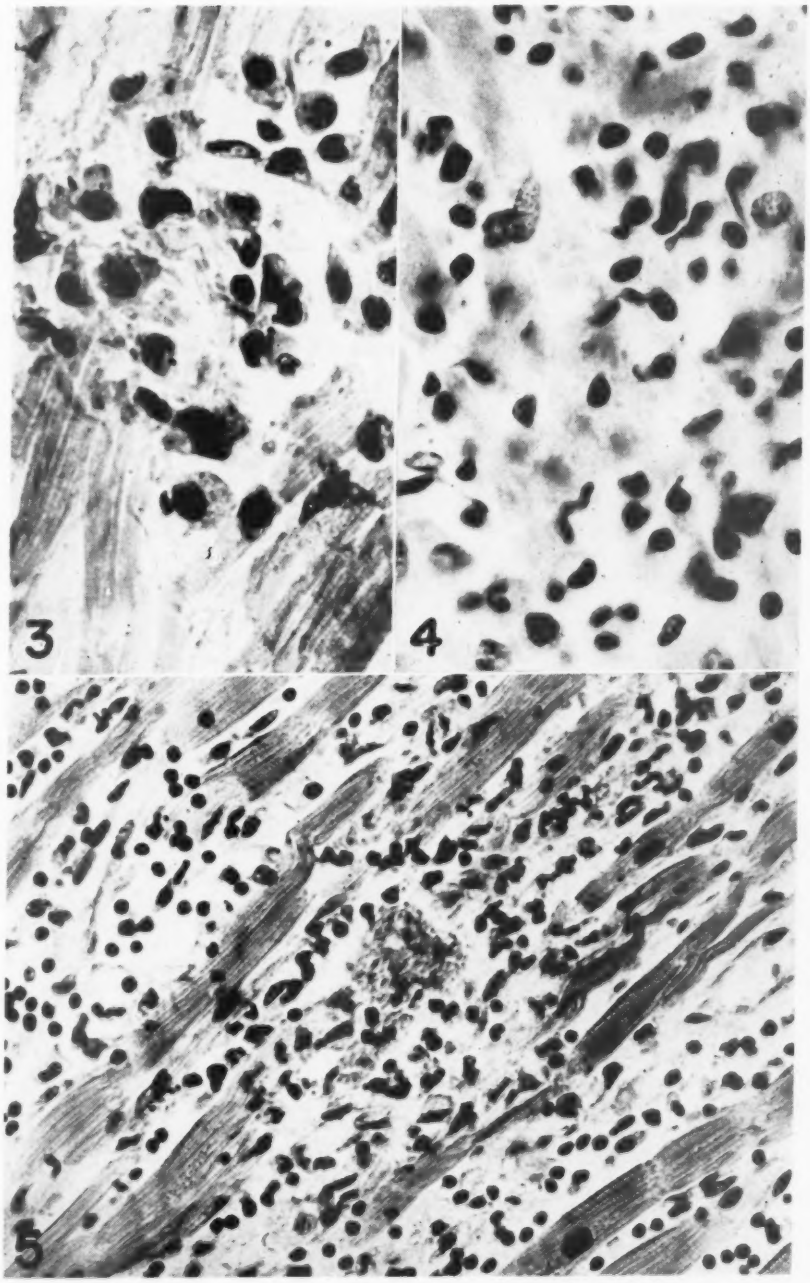

Fig. 3.—Case 29, AIP Accession 89356. Accumulation of monocytes, Aschoff cells, and macrophages, replacing muscle fibers. × 600. Neg. 95116.

Fig. 4.—Case 23, AIP Accession 165987. Early diffusely infiltrating myocarditis. Note shadows of muscle fibers in addition to the inflammatory cells. × 600. Neg. 95113.

Fig. 5.—Case 23, AIP Accession 165987. Diffusely infiltrating myocarditis. Note the necrosis of muscle fibers. Round cells predominate. × 435. Neg. 95125.

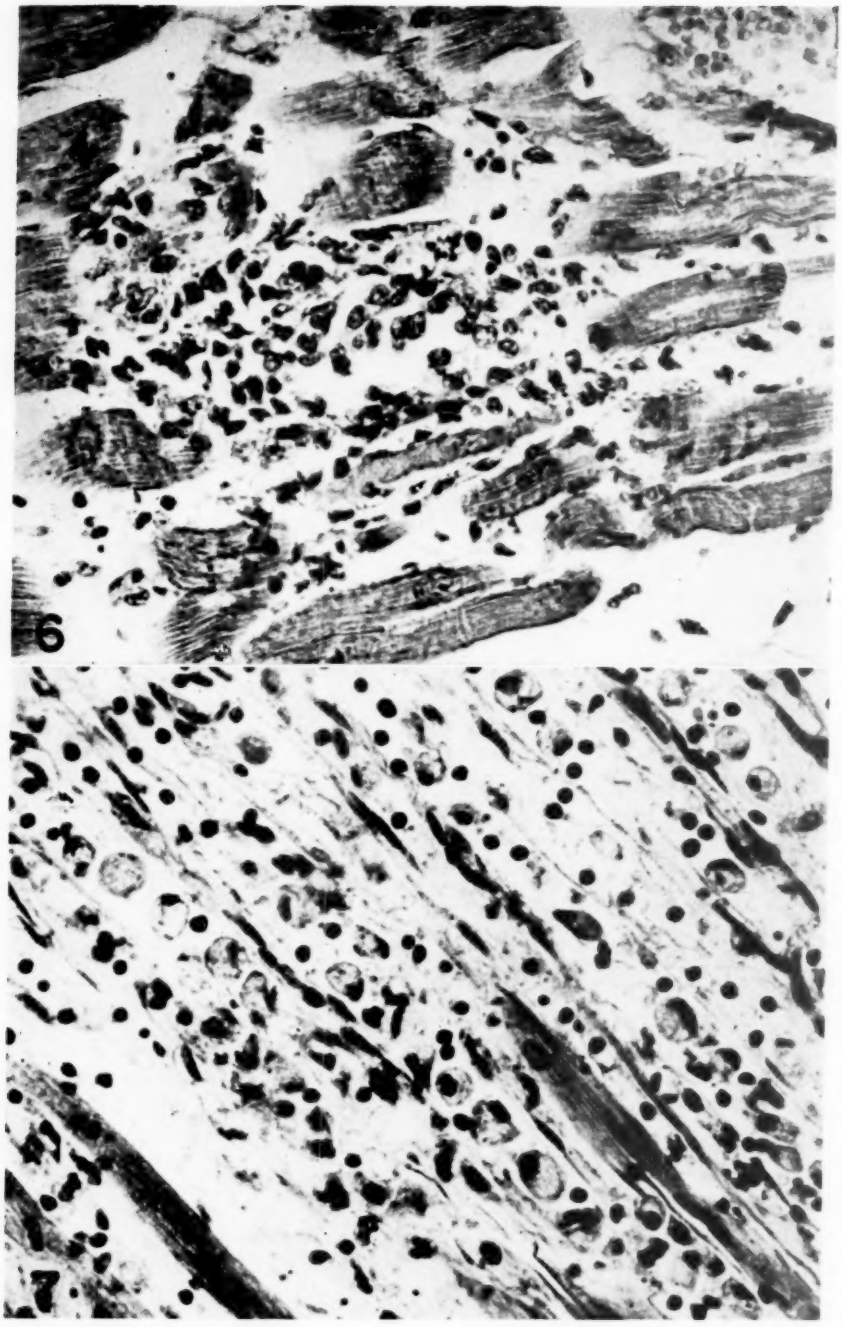

Fig. 6.—Case 31, AIP Accession 103378. Early "explosive" lesion showing an accumulation of endothelial leucocytes interrupting the course of a few heart muscle fibers. × 435. Neg. 95114.

Fig. 7.—Case 23, AIP Accession 165985. Numbers of plump macrophages are present in the stroma, persisting after the disappearance of heart muscle fibers. × 435. Neg. 95126.

the muscle and the stroma of the intrafascicular tissue and spilled over, to a variable extent, into the neighboring septa. It invariably was associated with necrosis of the cardiac musculature, which was of moderate degree or more in all except three of the nineteen cases of the diffuse type (Fig. 2). The second variety, the *interstitial* type, of which there were thirteen examples, was characterized by involvement of the interfascicular septal stroma in particular (Fig. 1). Muscle necrosis, which occurred in only three of this group was in each instance of mild degree and "explosive" type (Figs. 5 and 6). The last variant, which included three cases, was called the *mixed* type since it exhibited features of both of the others. In general, the estimated severity of the myocardial involvement was greatest in the diffuse histologic variety (see Table III). Both tonsillar and pharyngeal infections were represented in each type; however, the diffuse group included nine, the interstitial group two, and the mixed group one of the fatalities due to acute tonsillitis. In Table III the cases of each group are listed according to the severity of the myocarditis estimated in terms of plus signs as mild (1), moderate (2), and marked (3). It is evident from an inspection of this table that there is no correlation between the duration of the illness and the type or severity of the myocarditis. Fatalities occurred between 4 and 37 days, 7 and 24 days, and 3 and 23 days in each of the groups, respectively.

In the diffuse group where parenchymatous lesions were the rule, the state of disintegration, phagocytosis, and lysis of the necrotic muscle fibers served as a crude index of the duration of the disease (Figs. 7 and 8). Fibrosis, observed in eight cases and representing early healing, did not occur earlier than the thirteenth day. Considerable variation was observed, not only in the presence or absence of myocarditis in different areas of the myocardium but also in its severity and in its estimated duration. Hyalinized or granular necrotic muscle fibers with varying degrees of surrounding inflammation, occurring next to areas of almost complete myolysis, were suggestive of continued activity of the cardiopathic agent.

A similar patchy distribution of the cardiac lesion was observed in the interstitial variety of myocarditis. In that form there were no evident histologic criteria to indicate the duration of the process. Foci of collagenous necrosis were found in four instances of interstitial involvement and in one of the mixed group (Cases 3, 5, 29, 31, and 32) (Fig. 9). In the most striking of these was a prominent "palisade" reaction of large mononuclear (Aschoff) cells; however, the lesions did not have the perivascular position characteristic of the rheumatic nodule.

Increased weight of the heart in each of the three histologic variants appeared to be related to the intensity of the myocarditis. The respective incidence (expressed as the ratio of enlarged hearts to total number of hearts weighed) of augmented heart weight in the severe, moderate, and mild groups was 7:11, 5:15, and 2:5. In the group of "diffuse" parenchymatous lesions, naturally, the number of enlarged hearts was greatest, since a preponderance of the severe cases was in this group.

TABLE III. ANATOMIC AND HISTOLOGIC FEATURES OF MYOCARDITIS IN THIRTY-FIVE CASES OF ACUTE TONSILLITIS AND ACUTE NASOPHARYNGITIS

	DIFFUSE																			MIXED			INTERSTITIAL													
Case number	2	17	1	6	9	10	12	15	16	7	8	11	14	23	25	26	30	34	35	20	3	33	18	19	21	29	4	13	22	24	27	28	31	32	5
Severity*	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	2	2	3	1	1	1	1	2	2	2	2	2	2	2	2	3
Duration in days	4	5	4	10	14	14	17	5	5	13	14	17	3	8	8	9	17	33	38	7	5	24	6	6	7	16	5	3	7	8	11	14	19	23	8
Heart weight in grams	298	350	425	–	'N'	400	315	250	430	355	560	520	380	375	Enl	460	–	430	Enl	450	387	375	400	406	318	390	N	260	400	–	365	–	340	330	500
Cardiac dilation	–	+	+	+	0	+	0	+	+	–	+	+	+	+	+	0	0	+	+	+	+	+	0	+	+	+	0	+	+	+	+	+	+	+	+
Gross alterations of myocardium	+	+	+	+	0	–	0	+	0	–	+	+	–	+	+	+	0	+	+	+	+	+	0	0	–	0	0	–	+	0	+	+	+	0	0
Diffuse involvement*	1	2	1	2	2	2	1	2	2	1	3	1	3	3	2	3	3	3	3	1	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0
Muscle necrosis*	1	1†	1†	2	2	2	2	2	2	3	3	3	2†	3	3	3†	3	3	3	1	2†	3	0	0	0	0	0	0	1†	0	0	0	0	1†	1†
Interstitial involvement*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	1	1	1	1	2	2	2	2	2	2	2	2	3
Fibrosis	0	0	0	0	0	F	F	0	0	F	0	F	0	0	0	0	F	F	F	0	0	F	0	0	0	0	0	0	0	0	0	0	0	0	0

– Indicates lack of descriptive statement in the available records.
* Estimated as mild (1), moderate (2), and marked (3).
N Under heart weight represents normal.
† Listed with muscle necrosis indicates an "explosive" type of lesion.

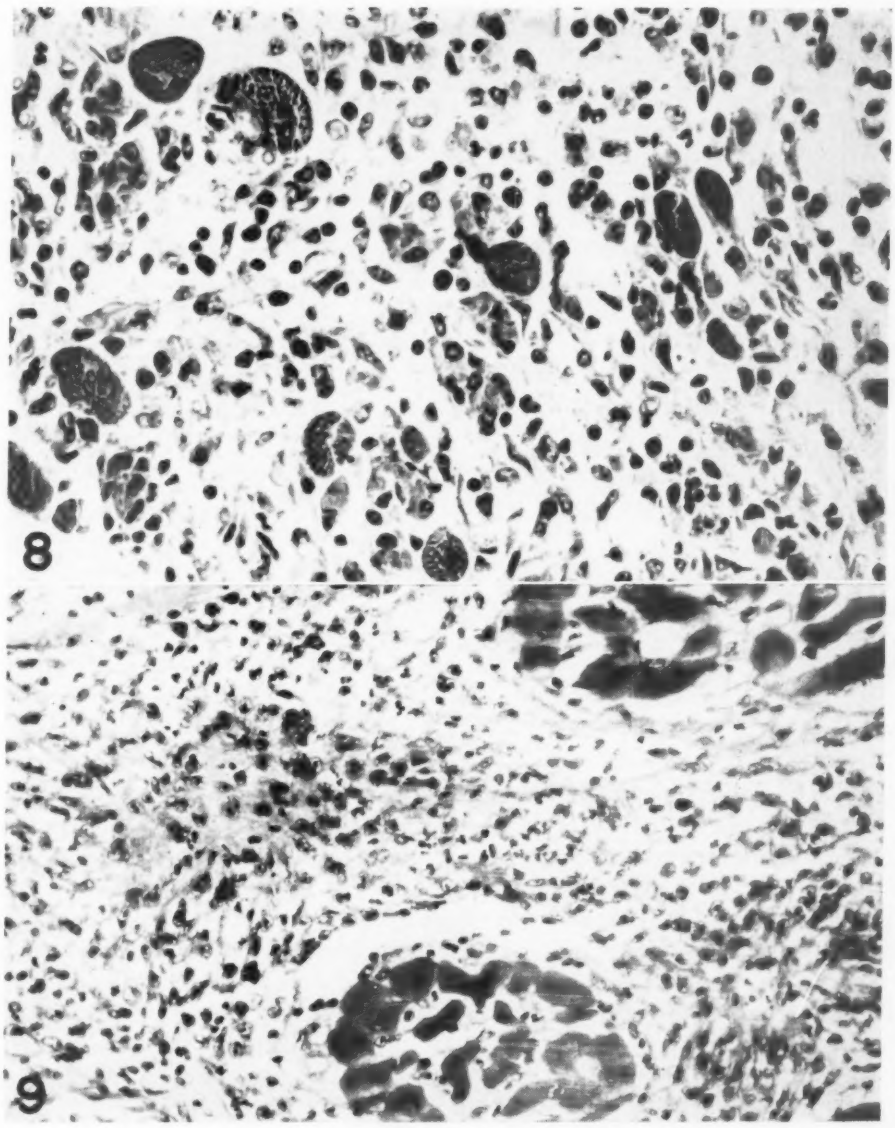

Fig. 8.—Case 34, AIP Accession 103357. Diffuse type of myocarditis. Lymphocytes, endothelial leucocytes, and a few polymorphonuclear leucocytes make up the inflammatory infiltrate. × 455. Neg. 95131.

Fig. 9.—Case 5, AIP Accession 139424. Two foci of "fibrinoid" necrosis of connective tissue occasionally found in the interstitial type of myocarditis. The palisaded cells are identical with those that contribute to the formation of the Aschoff nodule. Points which differentiate it from the latter are the lack of the characteristic perivascular position and the absence of giant cells. The cardiac valves, endocardium, and pericardium were intact. × 275. Neg. 95852.

The various clinical manifestations of heart disease and the frequency with which they occur in each of the three histologic variants are presented in Table IV. Although the figures are too small to be statistically conclusive, they suggest that hypotension and anginal pain are more frequent in the diffuse type of myocarditis. This again may merely be a reflection of the preponderance of severe myocarditis in that group.

TABLE IV. OCCURRENCE OF CARDIAC SYMPTOMATOLOGY IN THREE HISTOLOGIC TYPES OF MYOCARDITIS ASSOCIATED WITH ACUTE TONSILLAR AND ACUTE NASOPHARYNGEAL INFECTIONS

	DIFFUSE MYOCARDIAL LESION (19 CASES)	INTERSTITIAL MYOCARDIAL LESION (13 CASES)	MIXED TYPE OF MYOCARDIAL LESION (3 CASES)
Cyanosis	6	5	1
Dyspnea and/or orthopnea	7	7	2
Cheyne-Stokes respiration	1	1	0
Cardiac arrhythmia or irregularity	6	4	1
Disproportions of temperature and pulse	7	5	2
Hypotension and/or weak thready pulse	9	2	0
Anginal pain	5	1	0
Abnormal electrocardiogram	4	0	1
Unexpected death	7	6	2
Enlarged heart (x-ray)	3	1	1
Enlarged and tender liver	3	0	0
Pulmonary edema (terminal)	2	3	0
Dependent edema	1	1	1
Pulsus paradoxus	1	0	0

DISCUSSION

The clinical relationship between acute nasopharyngeal or tonsillar infections and subsequent acute rheumatic fever is well recognized. Little is known about any other cardiac complications. Lulled by the almost axiomatic teaching (which should be discarded) that "myocarditis other than that associated with acute rheumatic fever and diphtheria is for practical purposes nonexistent," the clinician has been almost oblivious to many inflammatory conditions of the myocardium. Seventy-five per cent of the cases of myocarditis in a series of 1,402 collected at the Army Institute of Pathology were nonrheumatic and nondiphtheritic. It has become increasingly evident with the more common use of the electrocardiogram that reversible, fleeting, or transitory alterations may occur during or shortly after a number of infectious diseases. The interpretation of the significance of such changes is considerably varied since a pathologic foundation is lacking. Estimates of incidence (cited in the introductory paragraphs) of cardiac involvement following the common cold and acute tonsillitis are in large part based on electrocardiographic studies.

Why should there be such a dearth of anatomic data in so prevalent a disease? First, and most fortunately for humanity, the death rate is undoubtedly very low, although further studies are necessary to establish the figure. A second reason is derived from the first: because death is not common and because central

laboratories of pathology are so few, it is rare for any one individual to have the opportunity to see more than occasional sporadic fatal cases. Following the too common practice, myocarditis has been considered idiopathic when rheumatic fever and diphtheria were ruled out, and, in the absence of a sufficient number of cases, correlation with a disease generally considered to be innocuous has been regarded as unreasonable. A third reason is, that because of the patchy distribution of the inflammatory process throughout the heart muscle, myocarditis has undoubtedly often been overlooked. The few blocks of myocardium routinely examined constitute but the crudest form of sampling; there can be no doubt that more thorough histologic examination of the heart would have uncovered a significantly greater number of lesions. Until the correlation with the antecedent infection is firmly established and a proper index of suspicion created, the clinician will continue to overlook many cases of myocarditis. As a matter of fact, the carditis was recognized clinically in only three of the cases forming the basis of this report (Cases 25, 33, and 35).

It is possible only to conjecture concerning etiology. The bacteriologic data available, which incidentally coincide with those generally accepted for acute tonsillar and nasopharyngeal infection, are sufficient only to cast the shadow of suspicion on the streptococcus as the etiological agent. The usual presence of this organism in the normal oral flora makes it difficult to evaluate its significance when isolated. Here is obviously a fruitful field for further bacteriologic study, using the streptococcal grouping and typing techniques developed by Lancefield.[5] The role, if any, played by the unidentified virus or viruses considered the primary etiological agent of the common cold is unknown. Nevertheless, controlled experimental infections of laboratory animals with the known viruses of respiratory infections have not produced myocardial lesions (Smadel[6]). Sulfonamides administered to twenty-six of the patients did not cause or appreciably contribute to myocarditis in this series, since the pathologic changes were the same as those in the hearts of patients who had no such medication. Furthermore, periarteritic and arteritic lesions of the type reported by Rich[7] and demonstrated by French[8,9] in the heart in sulfonamide hypersensitivity were absent from the cases reported here, as were also the visceral cellular infiltrates rich in acidophilic histiocytes and leucocytes. (Renal suppression in two patients resulted from the summated effects of circulatory failure and sulfonamides.)

Naturally, a full account of the pathogenesis is dependent on determination of etiology. But there are important implications in certain of our observations: absence of histologically demonstrable organisms in the myocardial lesions (Schenken and Heibner[10] have reported the cultural isolation of a streptococcus from the myocardium of a case of "isolated" myocarditis); predominance of mononuclear cells in the inflammatory response; and frequency of parenchymatous necrosis somewhat similar to that produced by diphtheria toxin. Although septicemia was ruled out, the possibility of transitory bacterial seeding must be taken into consideration; however, if such an event took place, organisms must have been destroyed rapidly. Our material does not permit us to comment

regarding the role of hypersensitivity, but the clinical data of Rantz, Boisvert, and Spink[1] indicate a striking relation between the frequency of recurrences of acute upper respiratory infections and the incidence of myocardial involvement.

Since myocarditis associated with these infections has been largely unrecognized to date, we do not consider it amiss to comment on the problems of prognosis and of therapy. In general, the prognosis should be viewed with a certain degree of optimism. Although there is good reason to suspect a high morbidity from this disease, the scarcity of pathologic data testifies to the low mortality rate. Even in the fatal cases, a striking tendency toward spontaneous cure is suggested by the presence of fibrosis as seen in a significant proportion of the hearts examined in this study.

The most rewarding field lies in the treatment of patients whose hearts have sustained an intermediate degree of damage. Complete rest diminishes the physiologic demands upon the heart. Certain of the cardiac stimulants, by increasing the efficiency of that portion of the myocardium which still retains functional capacity, may prolong survival to the point where the physiologic healing mechanisms have had a chance to cope with the inflammatory process.

Data in the clinical records of the cases we have studied make it clear that great care must be exercised in giving fluid intravenously. Intravenous administration of fluids, which at present is a routine and valuable procedure in the treatment of "common" shock where the heart is normal, may fatally overload a diseased heart which has become incapable of sustaining even normal blood tension. An increasing awareness on the part of the physician of the cardiac effects, not only of tonsillitis and nasopharyngitis but also of many other infectious diseases and processes, would lead to more frequent differentiation of cardiogenic shock for which intravenous fluids may be lethal from the more common variety of shock for which intravenous fluids may be lifesaving.

In reviewing these cases and others of postinfectious myocarditis, it becomes apparent that there is a feature of the disease which hinders clinicians and pathologists from associating the development of cardiac manifestations with the infectious process responsible for them. Heart symptoms often become evident at a time when the clinician and the patient have concluded that the primary disease process is under control, with the result that developments are frequently regarded as an independent process. Certain cases reported in the literature (erroneously, we believe) as Fiedler's or "isolated" myocarditis illustrate such a mistake. Frequently, the primary disease is considered innocuous just as is the common cold or acute nasopharyngitis. Nevertheless, in spite of a clinically "free" interval in such cases, the pathologic findings are in no way different from those without such an interval. A well-established clinical analogy exists in diphtheritic infections where it is recognized that myocarditis may develop after the demonstrable local inflammatory process has largely subsided. (See Cases 3, 6, 8, 9, 10, 11, 15, 21, 31, and 33.)

SUMMARY

Thirty-five instances of fatal myocarditis attributable to acute nasopharyngeal and tonsillar infections have been reported. The available evidence indicates that these are samples of a not uncommon type of cardiac disease which fortunately has a relatively good prognosis. Further investigation should be carried on to establish fully the etiological agent and the pathogenesis of the lesion. Although the pathologic observations indicated that all patients died of cardiac failure, heart disease was suspected clinically in only three, and in fifteen patients death was unexpected. Significant clinical observations which would seem to be of importance in the recognition of the process were: disproportion of the temperature and pulse rate, hypotension, thready or feeble pulse, and substernal oppression. Cyanosis, dyspnea, and orthopnea occurred frequently.

Autopsy findings included significant enlargement of the heart in many cases. The microscopic changes, similar in both nasopharyngeal and tonsillar infections, have been classified in three overlapping groups. In all of these the inflammatory process was observed to be patchy, frequently showing considerable variation in intensity from one area to another and having no predilection for a particular portion of the myocardium. Significant (moderate or marked) degrees of muscle degeneration observed in the diffuse type of myocardial lesion were not present in the interstitial form. The cellular reaction, which was characteristically more intense than that observed in diphtheritic myocarditis, was predominantly mononuclear, but significant numbers of polymorphonuclear leucocytes accumulated at sites of more severe inflammation.

Although the figures are too small to justify conclusions, there appears to be significant correlation between the clinical occurrence of hypotension and the estimated severity of the myocarditis, since it was a feature in every severe case in which the blood pressure was recorded. The only available electrocardiograms (four), abnormal in every case, were from patients whose hearts showed muscle degeneration of moderate or marked degree. Anginal pains were related to the presence of hypotension. Fibrosis of the heart muscle was related both to the muscle degeneration and to duration of illness.

In therapy, attention is called to the danger involved in the administration of intravenous fluids.

CLINICAL ABSTRACTS

Tonsillitis (Cases 1-12).—

CASE 1.—A.I.P. Accession 140817. A 37-year-old white man contracted acute tonsillitis while undergoing topical penicillin treatment for gingivitis. Sulfadiazine therapy was instituted but was discontinued on the third day, though the throat infection was still present. The temperature was 101°F.; pulse rate, 80; respirations, 20; and blood pressure 130/70. He was found dead in bed on the fourth hospital day.

CASE 2.—A.I.P. Accession 113630. A 24-year-old Negro man, admitted with complaints referable to hemorrhoids, was found to have mild acute tonsillitis. Temperature was 98.8°F.; pulse rate, 110; respirations, 24; and blood pressure, 104/60. Urinalysis and Wassermann reaction were negative; the white blood cell count was 7,000. Throat culture revealed streptococci and staphylococci. Weakness was a prominent clinical feature. The temperature on the

second day was 99°F., but both temperature and pulse rate rose on the third day. Blood culture was negative, white blood cells numbered 12,000, with 68 per cent polymorphonuclear cells. Roentgenograms on that day showed a slight increase of the hilar and peribronchial markings. Death occurred seventy-eight hours after admission to the hospital.

CASE 3.—A.I.P. Accession 106073. A 24-year-old white man was admitted to the hospital with moderate tonsillitis of two days' duration. The temperature was 101°F., the heart and lungs were clear. Sulfathiazole therapy was started on the first hospital day when the temperature was 102° Fahrenheit. The temperature dropped to 99°F., the tonsillitis appeared to be subsiding, and the patient appeared comfortable. The following morning he was found dead in bed. Throat culture revealed hemolytic streptococci.

CASE 4.—A.I.P. Accession 102488. A 25-year-old white man had had acute tonsillitis four months previously. On admission to the hospital his temperature was 97°F.; pulse rate, 80; respirations, 20; blood pressure, 130/80; and white blood cells, 9,600. Hypertrophic tonsils were removed under local anesthesia. On the second postoperative day there was considerable pain locally, the temperature was 99.6°F., and pulse rate was 74. Swelling of the neck and hemorrhage from the site of operation appeared on the third day as the temperature rose to 103.2°F., and the pulse rate to 88. Sulfadiazine was given. Cyanosis, dyspnea, restlessness, and irregularity of pulse developed the following day. Oxygen and tracheotomy provided no relief. White blood cells numbered 15,500, with 83 per cent polymorphonuclear leucocytes; blood culture was negative. Sulfathiazole was given intravenously, but there was no apparent response. On the fifth day the temperature was 102.8°F.; the pulse rate, 126; and the blood pressure, 145/90. Death occurred early the next morning.

CASE 5.—A.I.P. Accession 139424. An 18-year-old white man was admitted to the hospital with acute tonsillitis of one day's duration. His temperature was 99.8° Fahrenheit. Sulfadiazine was administered. When the temperature rose the following day to 104°F., sulfadiazine was augmented by penicillin. White blood cells numbered 27,000, with 90 per cent polymorphonuclear leucocytes. On the fourth day the temperature was 101°F. to 102°F., and white blood cells numbered 12,600. Throat culture yielded alpha streptococcus, *Staphylococcus albus*, and hemophilus. On the sixth day with the condition of the pharynx unchanged, there was x-ray and clinical evidence of bronchopneumonia. Temperature was 102°F., white blood cells numbered 9,000, with 88 per cent polymorphonuclear leucocytes. Cyanosis, dyspnea, and auricular fibrillation became evident. On the seventh day pulmonary edema developed and the patient died. The last recorded temperature was 102°F., with a pulse rate of 130 per minute.

CASE 6.—A.I.P. Accession 140417. A 31-year-old white man was hospitalized for acute tonsillitis and treated with sulfadiazine. On the second day the temperature was 99.6°F.; white blood cells, 23,000, with 90 per cent polymorphonuclear leucocytes. There was still a mild leucocytosis on the fifth day, the white blood cells being 12,600. The local process had largely resolved by the ninth day, when he complained of sudden pain. The heart sounds were rather poor, rhythm irregular, blood pressure 85/70, and radial pulse weak. The following day these manifestations persisted. The patient's color was ashen, respirations labored, temperature 101°F., and blood pressure was 70/?. Pulmonary edema was present. An electrocardiogram demonstrated ventricular tachycardia. Anuria noted on the last day of life was attributed to shock. Blood nonprotein nitrogen was 210 mg. per cent and the blood sulfa level was 1.6 milligrams. Postmortem blood culture was negative.

CASE 7.—A.I.P. Accession 146376. A 25-year-old white man had received sulfathiazole for nine days in treatment of tonsillitis. At that time the white blood cells numbered 4,300. On the eleventh day, a peritonsillar abscess developed. Throat culture was reported as negative for diphtheria. Heart sounds were faint with a reduplication of the first sound, the pulse of poor quality, blood pressure, 90/60, white blood cell count, 21,500, and sedimentation rate accelerated. There was no elevation of temperature. Death from circulatory failure occurred after a period of Cheyne-Stokes respirations and convulsions.

CASE 8.—A.I.P. Accession 164750. A 23-year-old white man was hospitalized on the third day of acute tonsillitis. Throat smear and culture were negative for diphtheria. Blood count showed a moderate leucocytosis with a "left shift" in the Schilling index. Treatment, which included penicillin and sulfadiazine, was stopped when the fever subsided, but leucocytosis of 14,000 remained. On the twelfth day of illness the liver was observed to be swollen and tender. The patient was cyanotic, heart sounds were distant, and blood tension low, 85/60. Death occurred two days later, following convulsions and Cheyne-Stokes respirations.

CASE 9.—A.I.P. Accession 125363. A 33-year-old German had acute rhinitis, acute maxillary sinusitis, and acute cellulitis of the face subsequent to tonsillitis. Temperature was elevated. Two blood cultures were sterile. Sulfadiazine and penicillin appeared to control the infection effectively so that the clinical status was described as good. On the fourteenth day the patient suddenly complained of chest pain. The heart sounds were poor, pulse thready, and arterial tension was 85/55. Death occurred in a short time.

CASE 10.—A.I.P. Accession 133950. A 24-year-old white man was admitted to the hospital with an acute peritonsillar infection from which hemolytic streptococci were cultured. White blood cells numbered 22,400, with 89 per cent polymorphonuclear leucocytes. Sulfadiazine was administered and the temperature which had been high reverted to normal by the fourth day. On the ninth day, during seeming convalescence, bradycardia and acute heart failure developed. Cyanosis and mild convulsive episodes followed. Leucocytes numbered 17,500, with 82 per cent polymorphonuclear cells. Throat smear and culture were negative for diphtheria. The blood nonprotein nitrogen was 115 and rose to 192 mg. per cent. Erythrocyte sedimentation rate was normal. Electrocardiograms showed daily variations, including auricular fibrillation and idioventricular rhythm. Death occurred on the fourteenth day.

CASE 11.—A.I.P. Accession 145824. A 21-year-old white man was admitted to the hospital with acute tonsillitis of one day's duration. The temperature was 104.8°F., the white blood cells numbered 11,800. Throat culture was negative for diphtheria. Sulfadiazine therapy was started on admission and was augmented by penicillin on the third day because tonsillitis persisted despite subsidence of the fever. Chemotherapy was stopped on the ninth day when the condition of the tonsils was improved, although they were still inflamed. Convalescence seemed uneventful until the sixteenth day when abdominal pain and vomiting started. Despite antishock measures to combat a weak thready pulse, poor heart sounds, and gallop rhythm, death occurred on the seventeenth day. The leucocyte count on the day of death was 15,500.

CASE 12.—A.I.P. Accession 104420. A 19-year-old white man was admitted to the hospital with acute tonsillitis of one week's duration. The leucocyte count was 19,800, with 85 per cent polymorphonuclear cells. Despite sulfonamide therapy, leucocytosis was progressive. It was 33,000 on the sixteenth day when evidence of bronchopneumonia was noted. Death occurred on the following day.

Acute Nasopharyngitis (Cases 13-35).—

CASE 13.—A.I.P. Accession 143838. An 18-year-old white man was hospitalized with acute nasopharyngitis and laryngitis of two days' duration. Overnight the temperature rose rapidly from 99.8° to 105° Fahrenheit. The pulse rate with that temperature was 110, the patient appeared extremely toxic and there was slight cyanosis. An early pneumonic process was present at the base of the right lung. Despite penicillin therapy, oxygen, and intravenous fluids, there was progressively increasing cyanosis; the pulse rate rose to 140 per minute and death occurred on the third day of illness, twenty-four hours after admission. Streptococci were cultured from the lungs and bronchi post mortem.

CASE 14.—A.I.P. Accession 89894. A 26-year-old white man was acutely ill with severe nasopharyngitis: temperature was 104.3°F.; pulse rate, 108; and respirations, 22 per minute. The white blood cell count, which was 23,000 the day following admission, fell to 13,300 on the second hospital day. Sulfadiazine therapy had to be discontinued because of an undue emetic effect. On the third day pulmonary edema developed and the patient died. A post-mortem culture of the heart blood was sterile.

CASE 15.—A.I.P. Accession 96506. An 18-year-old white man was hospitalized with an acute respiratory infection of thirty-six hours' duration. The temperature was 104°F.; pulse rate, 120; and respirations, 22 per minute. Under sulfathiazole therapy the temperature dropped overnight to 100.2° Fahrenheit. The pulse rate was 112; the white blood count 20,000. On the second day, improvement appeared progressive; temperature dropped to 99.4°F. and pulse rate to 90 per minute. Late that day, however, the patient became dyspneic, the pulse rate rose to 132, and death occurred suddenly in the early hours of the following morning. Hemolytic streptococci were cultured from the lungs post mortem.

CASE 16.—A.I.P. Accession 150897. A 33-year-old white man was hospitalized with an acute upper respiratory infection of one day's duration. The temperature was 102.4°F.; pulse rate, 100; and respirations, 20 per minute. The white blood count on the first hospital day was 18,000, and roentgenograms showed a small pneumonic patch at the base of the right lung; the temperature was 1 4.2° F., and blood pressure was 11 ½68. Despite sulphadiazine therapy, the pneumonic process extended, and on the third day the temperature was 104°F. and the pulse rate 120 per minute. Dyspnea and cyanosis were noted on the morning of the fourth day when the patient died. Penicillin was administered terminally. Streptococci had been isolated from the sputum and were also cultured from the lungs post mortem.

CASE 17.—A.I.P. Accession 114683. A 20-year-old white man was admitted to the hospital with a "cold" of two days' duration. Two and one-half months previously he had had a type I pneumococcal pneumonia which had responded well to sulfadiazine therapy and was without evident residua. Temperature was 99.4°F. and pulse rate 104 per minute. The temperature was 99°F. the next morning. The patient died suddenly sixty-five hours after admission.

CASE 18.—A.I.P. Accession 94336. A 40-year-old white man was hospitalized with an acute "upper respiratory infection" of six days' duration. The temperature was 102.4°F.; pulse rate, 96; and blood pressure, 115/70. Physical signs and roentgenograms indicated a pneumonic involvement of the bases of both lungs. The white blood cell count was 11,100. The pneumonic process had spread by the second day, when acute heart failure developed suddenly and the patient died. Therapy had included sulfadiazine.

CASE 19.—A.I.P. Accession 114270. A 38-year-old Negro was acutely ill with a three-day history of cough, chills, and fever. The admission temperature was 102.4°F.; pulse rate, 108 per minute; and white blood cell count, 30,500. Sulfadiazine was administered, but was discontinued and penicillin substituted when oliguria was observed on the first hospital day. Roentgenograms taken on admission disclosed pulmonary congestion and an enlarged heart. Death occurred on the third day when pulmonary edema suddenly developed.

CASE 20.—A.I.P. Accession 86952. A 24-year-old white man had a cough and sore throat of one week's duration. The temperature was 101°F. and the pulse rate 86 per minute. Three and one-half hours after admission the patient became restless, dyspneic, and cyanotic; coma developed, and death supervened within one-half hour.

CASE 21.—A.I.P. Accession 98439. A 19-year-old white man was hospitalized on the second day of an illness diagnosed as acute nasopharyngitis. The temperature was 104°F. and the pulse rate 120 per minute. Sulfadiazine therapy was instituted. After apparent clinical improvement, a pneumonic process, confirmed by x-ray, developed on the sixth day. The patient went into Cheyne-Stokes respiration and died the same day. At autopsy, pneumococcus, type XVII, was isolated from the heart blood; and identical organisms, as well as streptococci, were cultured from the lungs.

CASE 22.—A.I.P. Accession 135455. A 25-year-old white man was admitted to the hospital with "substernal oppression" which had developed on the fourth day of a "cold." Temperature was 99°F.; pulse rate, 84; and respirations, 18 per minute. Blood pressure was 94/64. The white blood cell count was 10,800 and the sedimentation rate was accelerated. Heart sounds were weak. Substernal pain and cough persisted and the following day the temperature was 105.2°F.; the

pulse rate, 108 per minute; and the respiratory rate was increased to 32. The lungs were clear to physical examination; a blood culture was sterile. Sulfathiazole therapy was instituted. Cardiac irregularity, consisting of extra systoles and paroxysmal fibrillation, was noted. Death occurred suddenly on the second hospital day, the seventh day of illness.

CASE 23.—A.I.P. Accession 165987. A 30-year-old white man was hospitalized on the seventh day of an acute infection of the upper respiratory tract. The temperature was 102°F. and the pulse rate was 140 per minute. There was moderate dyspnea and cyanosis and evidence of consolidation at the bases of both lungs. Penicillin and sulfadiazine were without evident effect. On the day following admission cyanosis and dyspnea were more marked, the pulse was weak and thready, and the patient died with pulmonary edema. Streptococci were cultured from the lungs, post mortem.

CASE 24.—A.I.P. Accession 76869. Early in the course of a mild "cold," a 25-year-old Negro had sudden pleuritic chest pain accompanied by hemoptysis. On admission to the hospital the temperature was 99.4°F.; pulse rate, 86; and respirations, 24 per minute. Blood pressure was 130/76. White blood cell count was 16,100. Sulfathiazole was administered when roentgenograms of the chest revealed irregular mottling in both lower lobes. During the succeeding days the pulmonary process spread and fluid accumulated in the left chest. There was progressive dyspnea, and death occurred with pulmonary edema on the eighth day of illness.

CASE 25.—A.I.P. Accession 139665. A 35-year-old white man noted orthopnea early in the course of a mild "upper respiratory infection." He was hospitalized on the fourth day because of "substernal pressure." The heart was enlarged. On the fifth day the pulse was found to be of poor volume, very irregular, and very rapid (168 per minute). Blood pressure was difficult to ascertain because of a pulsus paradoxus, but was recorded at 120/80. The veins of the neck were distended; the liver was tender. Temperature at this time was 98.6°Fahrenheit. Digitalis was prescribed. On the sixth day there was a slight pulse deficit (120 apical rate, 104 pulse rate) and the blood pressure was 110/86. Death occurred suddenly on the eighth day of illness. A culture of the heart blood, post mortem, was sterile.

CASE 26.—A.I.P. Accession 111927. A 32-year-old white man was admitted to the hospital on the fifth day of a "common cold." The temperature, which was 102.6°F. on admission, rose to 104.4°F. within a few hours. Pulmonary signs developed on the first hospital day. The white blood cell count was 7,100. Roentgenograms on the following day showed "either a central pneumonitis or congestive heart failure." The temperature was now 104°F.; the white blood count, 11,700. On the third hospital day (the eighth day of illness) there was cyanosis and dyspnea; the pulse was weak and rapid, the blood pressure was 84/70, and a gallop rhythm was present. An electrocardiogram demonstrated myocardial damage. The course was rapidly downhill and death occurred early in the morning of the ninth day. Blood cultures taken on the second and third hospital days were sterile.

CASE 27.—A.I.P. Accession 109627. A 25-year-old white man was admitted to the hospital with a rash and fever of five days' duration. A diagnosis of measles was made. The rash faded and the temperature subsided to normal by the second hospital day. On the third day, the temperature had risen again to 102°F. and a diagnosis of acute nasopharyngitis was made. On the fifth day, sulfadiazine was administered because of pleuritic chest pain. Pulmonary involvement was demonstrable in roentgenograms; the white blood cell count was 15,400; and hemolytic streptococcus was cultured from the sputum. There was progressive cyanosis and dyspnea, and death occurred following the development of pulmonary edema. At autopsy both heart blood and lung cultures were positive for the same streptococcal organism (Group A, type III).

CASE 28.—A.I.P. Accession 141224. A 20-year-old white man was admitted to the hospital with chest pain and dyspnea which had developed on the tenth day of acute nasopharyngitis. Dyspnea seemed far out of proportion to the signs of involvement of the chest. X-ray revealed "soft infiltration in the hilar regions." Therapy, which was without beneficial effect, included sulfadiazine and penicillin. The white blood cell count on the second hospital day was 6,300.

On the third day 600 c.c. of blood-tinged pleural fluid was removed from the chest but reaccumulated rapidly. There was marked ankle edema at the time of the patient's death on the fourth hospital day, the fourteenth day of illness.

CASE 29.—A.I.P. Accession 89356. A 43-year-old white man was admitted to the hospital after an acute "upper respiratory infection" of five days' duration. The temperature was 103.6°F.; pulse rate, 110; and respiration, 22 per minute. Blood pressure was 122 74. Sulfadiazine was prescribed. The white blood count was 7,400 and there was no clinical evidence of pulmonary disease on the third hospital day, although the temperature was still elevated. The white blood cell count on the tenth day of illness (fifth hospital day) was 6,000, the polymorphonuclear leucocytes showed a marked "left shift." Death occurred unexpectedly on the sixth hospital day, the eleventh day of illness, when restlessness, cyanosis, and dyspnea suddenly appeared.

CASE 30.—A.I.P. Accession 73793. An 18-year-old white man was admitted to the hospital on the twelfth day of an acute "upper respiratory infection." The temperature was 101.4°F.; the pulse, 130; and the blood pressure, 98/42. Roentgenograms of the chest showed essentially no pulmonary disease but did demonstrate cardiac enlargement to the left. Despite oxygen, increasing cyanosis and dyspnea were observed from the second hospital day. The course was febrile and progressively downhill; death occurred on the fifth hospital day. Sulfapyridine had been administered during hospitalization.

CASE 31.—A.I.P. Accession 103378. A 28-year-old white man was hospitalized on the second day of an acute pharyngitis. The temperature was 100°F.; pulse rate, 90; and respirations, 22 per minute. The white blood cell count was 11,600. The pharyngitis subsided by the second day, but sulfathiazole was given for an infected umbilical sinus which had been draining for seven weeks. The latter improved considerably, but on the fifteenth hospital day the pharyngitis recurred. The temperature was initially 101.6°F.; the white blood count, 9,900. The fever mounted rapidly to 105.4°F., the pulse rate was 158, respirations were dyspneic, and blood pressure was 90/50. This state persisted, accompanied by drowsiness and mild diarrhea, and death occurred unexpectedly on the sixteenth hospital day.

CASE 32.—A.I.P. Accession 86959. A 25-year-old white man was admitted to the hospital on the second day of an acute nasopharyngitis. The temperature was 102°F.; pulse rate, 100; respirations, 20 per minute; and blood pressure, 118/60. The course was febrile, with temperatures ranging from 101° to 104° Fahrenheit. Pulse and respiratory rates gradually increased. Blood counts showed a relative leucopenia; the white blood cell count rose to a maximum of 16,000, but ranged between 8,000 and 12,000. Despite sulfathiazole and sulfadiazine, a pneumonic process originally limited to one lobe spread bilaterally. On the fifteenth day progressive weakness was observed; there were episodes of irrationality. Fatal pulmonary edema developed on the twenty-third day. At autopsy a streptococcal organism was isolated from the heart blood, the lungs, and the paranasal sinuses.

CASE 33.—A.I.P. Accession 93680. A 22-year-old white man returned to the hospital because of a pneumonic process four days after his release, after hospitalization for an acute upper respiratory infection. The temperature was 105°F. and the white blood cell count was 26,000. There were severe dyspnea and pleuritic pain. On oxygen and sulfathiazole therapy there was evident improvement. Although the fever subsided, pleural effusion developed on the third day. On the ninth day roentgenograms demonstrated partial resolution of the pneumonia, but there was enlargement of the heart. A soft to-and-fro murmur was present apically, and although there were no signs of cardiac failure, respirations were dyspneic, blood pressure was 104 58, and white blood cell count was 22,000. Electrocardiograms subsequently demonstrated myocardial damage and a heart rate of 146 per minute. Moderate left ventricular failure was diagnosed on the twelfth day. The temperature rose to 103°F. and the pulse rate to 90 per minute on the thirteenth day; the white blood count rose to 33,000 on the fifteenth day. Digitalization was undertaken on the seventeenth day when the patient presented dyspnea, orthopnea, and a pericardial friction rub. Heart action was irregular and rapid one day prior to death on the twenty-fourth hospital day.

CASE 34.—A.I.P. Accession 103357. A 24-year-old white man was hospitalized with a recurrence twenty-two days after a previous acute nasopharyngitis. The presenting symptoms included "chest pain." The temperature was 101.2°F.; pulse rate, 78 per minute; and respirations, 18 per minute. The heart and lungs were considered normal. Therapy consisted solely of sedatives which appeared to give relief. On the morning of the second hospital day the patient had a slight nose bleed and died suddenly of acute heart failure.

CASE 35.—A.I.P. Accession 157669. A 24-year-old white woman was hospitalized because of ankle edema. The patient had not felt entirely well since an acute "upper respiratory infection" two weeks previously. There had been orthopnea of one week's duration and constrictive sensation in the chest shortly before admission. The temperature was 98.6°F.; the pulse, 108; and the blood pressure, 94/82. Heart sounds were distant and the liver appeared enlarged. With bed rest the ankle edema subsided. On the sixth hospital day there was a sudden episode of vomiting, dyspnea, and cyanosis, associated with venous distention and swollen liver. An electrocardiogram indicated myocardial damage. A roentgenogram two days later showed the heart to be enlarged. White blood cell counts varied from 6,500 to 13,900. Blood cultures were sterile. Digitalization was instituted on the tenth day, but on the fifteenth day there was embolic occlusion of the right external iliac artery. Despite embolectomy, gangrene of the foot set in. Dyspnea and orthopnea persisted, the pulse remained poor, and death occurred on the twenty-fourth hospital day, thirty-eight days after the initial respiratory infection.

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ON THE ETIOLOGY OF CLUBBING OF THE FINGERS*

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IN MANY diseases clubbing of the fingers is a typical or an occasional feature, but the mechanism is disputed. Because of the uncertainty of pathogenesis and because of its diagnostic significance, this lesion has engaged the interest of physicians for a long time. Numerous theories of its causation have been proposed: toxic, neuritic, mechanical, static, anoxic, and so on. No theory has gained wide acceptance. Today the situation recalls one which led Osler to remark: "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future." This paper will attempt to take stock of known facts and indicate progress toward a final explanation for the mechanism of clubbing. The theory proposed is based on easily observed and generally accepted clinical data. It emphasizes the necessity for considering a cause of local anoxia which in the past has been disregarded, and points out a common basis for tissue anoxia in a galaxy of conditions in which cyanosis is not a feature. It is precisely this heterogeneous, apparently unrelated group of infections and neoplasms that gave rise to the abundance of theories when it appeared that the anoxia theory applicable in cyanotic heart disease was untenable in other conditions. If local anoxia can be shown to exist in these diseases, infections and neoplasms, it will make possible a return to a single pathogenic mechanism for clubbing of the fingers in a variety of diseases.

That clubbing exists in chronic arterial anoxia is an accepted fact. In congenital heart disease clubbing is seen only in the cyanotic group and in cyanose tardive only after the cyanosis has become established. When it is observed in other types of heart disease it is usually the result of chronic sepsis or severe pulmonary disease. In pulmonary emphysema clubbing occurs only when there is pronounced cyanosis or superimposed infection. Clubbing is present in individuals who for long periods of time have resided at high altitudes. It is also seen in some instances of aortic and subclavian aneurysms. Clubbing is also present in chronic methemoglobinemia, sulfhemoglobinemia, in enterogenous cyanosis,

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*For simplicity of usage, this term shall include associated clubbing of the toes and pulmonary osteoarthropathy.

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and in those chemical alterations in the hemoglobin which prevent its efficient use as a carrier of oxygen. In this respect these entities resemble somewhat the situation to be described, in which, however, interference with gaseous exchange is due to physical rather than chemical alterations which impair the usefulness of the hemoglobin. That anoxia exists in the conditions listed is apparent. However, tissue anoxia has not been recognized as a possible concomitant of infections and neoplasms. Yet it may be deduced that it exists in them, albeit the circulation is not obstructed and even in the finger tips cyanosis is not evident. It is the thesis of this paper that in certain infections and neoplasms in which clubbing makes its appearance, local tissue anoxia results from a peculiar physical state affecting the erythrocytes and evidenced by the increased sedimentation rate of the blood.

It is well known that the sedimentation rate of the blood is increased in infections and neoplasms in which clubbing exists: pulmonary tuberculosis; subacute bacterial endocarditis; bronchiectasis; empyema; lung abscess; chronic infections of the bowel, such as idiopathic ulcerative colitis, chronic dysentery, and regional enteritis; and in various neoplastic processes such as intestinal polyposis, bronchiogenic carcinoma, gastrointestinal malignancies, and large carcinomata of the breast. In the neoplastic lesions the elevated sedimentation rate is the result of tissue autolysis, infection, or both. But it is also recognized that clubbing does not occur in certain long-standing infections and in other lesions associated with increased sedimentation rates. These will be discussed.

The sedimentation rate of the blood, as an isolated phenomenon, is a reaction of a high degree of nonspecificity. The mechanism of the settling of the corpuscles is, however, of great importance. In general this acceleration is mainly a reflection of the level of the blood fibrinogen and, to a lesser extent, of the globulins.[1-3] The sedimentation rate varies directly with the concentration of these proteins. Increasing levels of the blood fibrinogen and globulin in some manner (altered colloidal state of plasma, changes in cellular charge, and so forth) cause the red cells to "stick together" and result in the formation of rouleaux. These aggregations of cells present to the surrounding fluid medium an increase in mass and a reduction in surface. This change and the reduction in the number of falling particles lead to increased rate of fall. (Other factors which influence the sedimentation rate are not germane and will be omitted from this discussion.)

Fahraeus[1] anticipated the question of the "biological importance" of rouleaux formation. "The qualification for this being the case is that the aggregations . . . at least under certain conditions . . . are an intravital phenomenon." In order to prove this he selected patients with increased sedimentation rates and demonstrated rapid settling of the red cells in artificially obstructed superficial veins. More important, he saw aggregates of red cells flowing through their retinal vessels and commented on the increased rate of flow in these individuals. At his suggestion, Ploman,[4] an ophthalmologist, studied the character of the blood flow in retinal vessels while applying pressure to the eyeball for short periods. He was so impressed with his observations on clumping of cells in vivo that in 1920 he was impelled to write that he was "surprised that the peculiar

and striking picture . . . is not more generally observed and known." Foord[5] described an identical observation in a patient with multiple myeloma in whom the marked in vitro rouleaux formation suggested the correct diagnosis. Fahraeus also studied the capillaries of the nail fold. A uniform flow of blood was seen in normal individuals; in those with increased sedimentation rates, varying degrees of granularity were present and the flow of colored material was broken by stretches of clear plasma. Knisely,[6] whose experience in the observation of the living circulation is extensive, states that in small laboratory animals rouleaux formation is not seen in the flowing blood "except under known pathological conditions such as ether anaesthesia, pressure or tension on the tissue, trauma, or preceding the death of the animal." Others also have observed this phenomenon in vivo. Wright and Duryee,[7] observing clumps of cells in capillaries, considered this proof that capillaries may be much wider than generally supposed. It is of interest to note that Duken and von den Steinen[8] not only observed granular flow but remarked on its presence in chronic pulmonary disease and in clubbing of the fingers. Ponder[3] states that this capacity for aggregation presents a real transfusion hazard: "A greatly increased tendency to rouleaux formation in the blood of a recipient suffering from an acute infective condition may sometimes give rise to great difficulty in securing a proper crossmatch with the cells of a donor of the same blood group, for extensive rouleaux formation is produced by proteins of the recipient's serum. These rouleaux may be so large and so stable that severe reactions result." Clinical examples of the difficulties engendered by autoagglutination are described by Foord,[5] Reiman,[9] and Belk.[10] Belk's experience led him to state that on occasion what was needed was "a different recipient, not a different donor." Thus it has been demonstrated that the erythrocytes of flowing blood are not always discrete structures, but may be bound together in rouleaux. We may now discuss their relation to tissue anoxia.

The biconcave configuration of the erythrocyte provides a structure admirably suited to its respiratory function. It results in the largest effective surface area in contact with plasma and facilitates efficient gaseous exchange. Individuals with normal sedimentation rates (normal fibrinogen, and so forth) have circulating red cells which are either discrete or form themselves into delicate rouleaux which disintegrate in the blood current. Thus, in health, the maximum cell surface area is made available for respiratory exchange. It is apparent that the functions of the red cells which have lost this ideal configuration by reason of aggregation into rouleaux will suffer in this regard. Gaseous exchanges at the periphery and perhaps in the lung will be interfered with in accordance with the number of cells in each clump, and, therefore, in proportion to the level of blood fibrinogen, and so forth, and the rate of sedimentation.

Fahraeus,[1] in 1921, pointed out this result of altered suspension stability. "That which is of greatest interest from a physiological point of view is, of course, the state of the corpuscles within the capillary system where in the service of respiration they exercise their most important physiological function, the gas exchange. The gas exchange between the corpuscles on the one hand, and the tissues and the alveolar air on the other, takes place via the plasma. As the aggregation of the corpuscles reduces the surface between the corpuscles and the

plasma, we must a priori conclude that it affects the gas exchange of the corpuscles in an unfavourable manner." How unfavorable this reduction in surface may be can be realized by visualizing rouleaux which, when large, comprise many cells, their broad surfaces apposed, forming extensive ropes enclosing lakes of plasma. The degree of stability of the rouleaux is graphically presented by Fahraeus in his description of slide preparations. "In normal blood, the corpuscle rouleaux fall apart at the slightest movement in the fluid, while the aggregates in the rapidly settling blood are not disturbed until very violent currents are produced. The rouleaux are strained and stretched like rubber tubes before they break. It is almost impossible through pressure on the cover glass to obtain complete disaggregation. The aggregates are consequently not only larger in the rapidly settling blood, but have besides a decidedly more solid structure. Another characteristic difference is that the formation of new rouleaux after disaggregation proceeds very much faster in the last-named kind of blood than in normal blood." There are, then, two factors which influence the respiratory surface in this abnormal state of the blood: the size of the rouleaux and their frangibility.

It is apparent that the rouleaux must traverse the circulation and it is clear that if they are large enough and sufficiently stable they will obstruct capillaries. Transfusion reactions due to rouleaux have already been mentioned, and Fahraeus discusses their relation to thrombi in acute infections and eclampsia. Foord[5] thought it possible that, in addition to the plugging of the tubules by protein in multiple myeloma, the obstruction of glomerular capillaries by clumping of red cells might contribute to the renal insufficiency of this disease. That rouleaux do exist in the flowing blood without causing obstructive phenomena has been observed and it is with this group that this paper is concerned. The comment of Wright and Duryee[7] on capillary width has already been cited. Many investigators, among them Haldane among Priestley,[11] Hooker,[12] and Krogh,[13] have pointed out the association of vasodilatation with anoxic states; and Mendlowitz[14] in his studies of the peripheral blood flow in individuals with clubbing found it to be augmented. Charr and Swenson[15] recently studied six instances of clubbing of the fingers and supplied pertinent data in five. Three patients with pulmonary tuberculosis came to autopsy, and the vessels of their hands were injected with radiopaque material. "The arteries and arterioles were more numerous, their lumens wider, and the ungual processes were covered with a heavier network of arterioles." Two patients, one with bronchiectasis and the other with congenital pulmonary stenosis, were studied by means of infrared photographs which revealed marked prominence of the superficial vessels. These accumulated observations indicate that the peripheral vascular bed is dilated in anoxic states and the arteriovenous anastomoses and bridges may well be utilized to accommodate the circulating rouleaux.

In recent years a new theory based on increased blood flow at the periphery has been proposed. Mendlowitz[14] observed it in clubbing of the fingers occurring in the wake of congenital heart disease and infections, and described the accompanying vasodilatation. He concluded, in 1942,[16] "that increased peripheral flow will form a cornerstone of the future theories on the mechanism of clubbing and hypertrophic osteoarthropathy." That this factor is important has already

been indicated. But it does not appear to be of initial importance, as without an anoxic factor clubbing does not occur. Clubbing is not seen during the course of hyperthyroidism, nor does it appear after sympathectomy. In view of the fact that dilated peripheral beds accompany anoxic states, it seems reasonable to assume that the increased peripheral flow observed by him is the result of vasodilatation secondary to the anoxia which exists in patients with clubbing. Mendlowitz and Leslie[17] produced cyanosis in dogs by means of a venoarterial shunt (anastomosis between the pulmonary artery and the left auricle). In one animal, after an interval of eight months, periosteal proliferation was observed in the ulna. They concluded that they had produced hypertrophic osteoarthropathy and attributed it to the increased systemic flow incident to the shunt. They stated that arterial anoxemia existed, but concluded that anoxia was not the cause of the bone change because "transport of oxygen to the tissues was normal because of the increased blood flow and oxygen consumption remained unchanged." It does not seem permissible to ignore the anoxia observed in this experiment, since arterial anoxia is so definitely related to symptomatology in similar diseases of man in which tissue oxygen tension is reduced and in which clubbing is so commonly found. When clubbing of the fingers occurs in congenital heart disease, it does so only after cyanosis is manifest. Here it is hardly conceivable that the delivery of oxygen to the tissues is unchanged. Rather, increased peripheral flow is a response to the anoxic state of the blood and tissues. More direct evidence is found in the observations of Blalock and Taussig[18] that clubbing recedes in their patients operated on for the tetrology of Fallot. Certainly this recession cannot be attributed to reduced peripheral flow, per se, incident to deflection of blood from the arterial system to the pulmonary artery. Obviously another factor must be operative, and it would appear reasonable to assume that the remarkable increase in oxygen saturation and the amelioration of dyspnea and cyanosis must be related to the reversal of clubbing seen in these subjects. The same reversal of clubbing occurring when individuals remain at sea level after prolonged residence at high altitudes is another expression of the role of increased oxygen tension in the tissues. Nevertheless, increased peripheral flow is an important factor in the production of clubbing in which the tissue anoxia is due to rouleaux formation. It may be that, due to the increased rate of flow, the rouleaux pass through the tips of the extremities with such rapidity that they do not have time to diffuse out their oxygen content. It is possible that many of the rouleaux escape through the arteriovenous anastomoses which are so numerous in these locations. The finger tips of subjects with clubbing are warm, and the factors of tissue warmth, speed of flow, and rouleaux formation all seem to be concerned with the delivery and uptake of oxygen by the tissues. As will be shown, tissue anoxia with cold finger tips and slow rates of flow is not conducive to clubbing.

In chronic rheumatoid arthritis the sedimentation rate is increased over periods of years and clubbing is not observed. But here, peripheral vasoconstriction and cold finger tips are the rule and the sluggish flow may be adequate to maintain oxygen tension in the acral tissues with low metabolic levels. More difficult to explain is the absence of clubbing in Raynaud's disease and Buerger's

disease, where chronic anoxic injury is only too apparent. But in these conditions as well the tissue temperatures are low and the blood flow is diminished. These stand in contrast to the conditions in which clubbing develops and in which the fingers and toes are warm and the blood flows are rapid. Whether such a mechanism is responsible for the rarity of clubbing in multiple myeloma cannot be stated at this time.

That clubbing of the fingers does not occur in anemia has been pointed out by critics of the anoxia theory. Anemia of a degree sufficient to cause tissue anoxia rarely persists for a long period of time, and it is well known that only the most severe anemias are associated with dyspnea at rest. In the absence of infection, the circulating red cells are discrete, exposing their entire surfaces to the plasma, or exist in the form of delicate, easily disintegrated rouleaux. Furthermore, in anemia the compensatory mechanisms are highly efficient. There is increased cardiac output, circulation rate, and local vasodilatation. The cells are fully saturated with oxygen in the lungs and by virtue of increased volume of flow are permitted to deliver it at effective pressure. Such protective mechanisms are of little value in conditions which prevent normal uptake and delivery of blood gases by the red cells. Chronic methemoglobinemia and sulfhemoglobinemia, rather than anemia, may be compared with the rouleaux effect and here again clubbing is observed.

Granting the preceding effects of rouleaux, of increased peripheral flow, and of shunts between arterioles and venules which are most numerous in the extremities, local tissue anoxia may exist in infections and neoplasms in which the red cells readily form rouleaux. It is to be expected that tissue alteration incident to such a mechanism would be influenced not only by the degree of physical alteration of the blood, but by the length of time during which it is operative, and undoubtedly by the degree of continuity of the process. This concept is of importance, since it probably explains the failure of clubbing to occur in all instances of a particular disease.

As has been stated, the "toxic" and "infectious" theories have been discarded, and properly so. Nevertheless, clubbing of the fingers is frequently associated with chronic infections. It has been seen to vary with the intensity of the underlying process, and indeed, has disappeared completely when cure has been attained. As one peruses a compilation of chronic infections in which clubbing has been described, he encounters lesions of diverse etiologies involving almost every system. Even the liver fails to escape inclusion; it is noteworthy that clubbing is described in cholangiolitic processes but is rarely found in cirrhosis, a lesion in which fibrinogen production is impaired.

The mechanism just described accounts for the production of clubbing of the fingers on a basis of tissue anoxia rather than on the transparent fact that intoxication is present. The arguments which have been used against the toxic theory seem to substantiate the mechanism proposed. It has been said that clubbing does not occur in chronic osteomyelitis unless there is amyloid disease. It has been suggested that here the clubbing is due to the amyloidosis. It seems more probable that the amyloidosis and the clubbing are both incident to the same process and both may be related to the high levels of plasma fibrinogen and

globulin. The theory proposed herein serves to explain the failure of clubbing to appear uniformly in infections of long standing. Instances of tuberculosis and bronchiectasis of many years' duration have been observed in which clubbing is not present. These are the individuals with little or no systemic reaction, low fibrinogen and globulins, and normal sedimentation rates.

It may well be asked whether clubbing of the fingers is the sole manifestation of chronic anoxia in conditions characterized by increased rouleaux formation. Individuals with severe cyanosis due to heart disease, and so forth, and those suffering from chronic mountain sickness, adapt themselves to the lower oxygen tensions of their blood. Yet in this process adaptation is only relative. In addition to clubbing they suffer from other symptoms of anoxia, such as dyspnea on exertion, loss of strength, easy fatigability, gastrointestinal disturbances, and certain psychologic abnormalities. Whether some of the poorly understood general symptoms of chronic diseases are related to the anoxic state invites further investigation. Since the time of Bert,[19] various students of anoxia have felt that in addition to the demonstrable cardiac, hemic, and respiratory adjustments of acclimatization, a tissue factor exists which permits satisfactory function at lower levels of oxygen saturation. Haldane and Priestley[11] state that despite lack of experimental verification there are facts which indicate the validity of this theory. Of morbus caeruleus they write "It seems hardly possible to doubt, therefore, that their tissues have become adapted to the low partial pressure of oxygen; and the same adaptation probably exists in many chronic cases of valvular heart disease, emphysema, etc." As Henderson[20] has succinctly written: "There are as many acclimatizations as there are altitudes at which a man can live." In infections and neoplasms a similiar latitude of adaptation exists.

Proof of this theory appears as difficult now as in 1923 when Lundsgaard and Van Slyke[21] bemoaned the difficulties encountered in the determination of tissue gas tensions. This factor is crucial in relation to the theory postulated. Isolated observations of the sedimentation rates and blood protein patterns are of little value. Therefore, no clinical observations are appended. Such as have been made seem to agree with the theory proposed. Unidigital and congenital clubbing are not discussed, since the author has not had the opportunity to study examples of these conditions.

SUMMARY

Clubbing of the fingers and toes, and the more severe "pulmonary" osteoarthropathies and periostitides, occur when there is arterial anoxia due to congenital or acquired lesions or residence at high altitude. It occurs in many disorders in which the erythrocyte sedimentation rate is rapid, but arterial oxygen saturation normal. In all these cases the vascular bed is wide, blood flow rapid, and the tissue warmer than normal.

That rapid sedimentation rates, with intravascular rouleaux formation, interfered with oxygenation of the tissues by decreasing the diffusion surface per unit of hemoglobin had long ago been suggested by Fahraeus. In this review it is suggested that with escape of rouleaux through the arteriovenous anastomoses

so numerous in the fingers and toes, rapid blood flow and high levels of arterial and venous oxygen saturation may be present simultaneously with low oxygen tension in the digital tissues. Thus, rapid rates of blood flow and low tissue oxygen tension would provide the same mechanism for clubbing in chronic infections, neoplasms, or metabolic defects leading to abnormal fibrinogen and globulin levels, as in the classical cases of arterial anoxia.

The most rapidly evolving and the most severe types of osteoarthropathy are seen in cases of mediastinal and lung tumors where the sedimentation rates are rapid and arterial anoxia is present. Here the two types of anoxia may coexist.

In rheumatoid arthritis, in Raynaud's disease, and in Buerger's disease clubbing is rare, although tissue anoxia is severe in the latter two and rapid sedimentation rates are characteristic of the former. But in all of these, blood flow and tissue temperatures are low in the tips of the extremities. It is thereby concluded that for the development of clubbing low oxygen tensions must occur in tissues which are warm and in which the blood flow is greater than normal.

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INHIBITION OF PAROXYSMAL VENTRICULAR TACHYCARDIA BY ATROPINE

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IT HAS been recognized that paroxysmal ventricular tachycardia can be induced by chloroform and by cyclopropane anesthesia in man. It can also be induced in animals anesthetized with these agents, especially after administration of sympathomimetic drugs.[1-5] The subject has been extensively reviewed by Meek[6,7] and it has continued to be the basis of more recent work.[8-20]

In the course of certain studies on the effects of sympatholytic agents in trained unanesthetized dogs we noted that the intravenous injection of epinephrine produced paroxysmal ventricular tachycardia. Because of the simplicity of the method and the advantages which we obtained by studying the effect of this ectopic initiating mechanism of epinephrine, we undertook a study of certain aspects of ventricular tachycardia. Attention was directed especially to the prophylactic benefits of atropine.

METHODS

Thirty-two experiments were performed on eleven young and mature dogs weighing 6.4 to 29.5 kilograms. Two had Goldblatt renal artery clamps and nine were unoperated. These dogs had been trained for a period of months to lie quietly while a needle was being inserted in the femoral artery and blood pressure was being recorded. Accordingly, the administration of the injections occasioned no observable discomfort or excitement in the animals. Electrodes were applied to shaved areas on the legs and electrocardiographic records were obtained with a string electrocardiograph; Lead II was used. After a control reading, a needle was inserted cephalad into the foreleg vein and a few cubic centimeters of normal saline were injected. After ten to thirty seconds the syringe was exchanged for one containing 1.0 mg. of epinephrine hydrochloride in 5.0 c.c. of normal saline and the solution was injected rapidly. A continuous recording was made of the period before, during, and for several minutes after the injection of epinephrine. A signal on the record indicated the beginning and end of injection.

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RESULTS

The Effects of Epinephrine.—The results are summarized in Table I. During the intravenous injection of epinephrine a rise in blood pressure occurred. Within twenty or thirty seconds the dog licked its lips and showed some signs of apprehension. At this time a slowing of the heart appeared, doubtlessly due to a reflex from the carotid sinus moderator mechanism (Fig. 1). The dog then appeared to relax and sometimes became apneic for ten to twenty seconds. In from 2 to 180 seconds after the end of injection, usually when the blood pressure showed signs of leveling off or had begun to decline, the marked reflex vagal bradycardia, which was often associated with sinus bradycardia (Figs. 2 and 7), sinus

TABLE I. DATA ON EPINEPHRINE-INDUCED PAROXYSMAL VENTRICULAR TACHYCARDIA

DOG	WEIGHT (KG.)	EXPT. NO.	DURATION OF EPINEPHRINE INJECTION (SEC.)	TOTAL DURATION OF EPINEPHRINE-INDUCED VENTRICULAR TACHYCARDIA (SEC.)
A	15.5	1	13.0	302
		2	8.0	11
		3	4.0	79
B	29.5	1	6.0	94
		2	10.5	70
		3	9.5	30
C	8.4	1	14.0	71
		2	4.5	168
		3	16.5	112
D	13.2	1	8.0	18
		2	4.0	30
		3	7.0	36
E	10.0	1	4.5	188
		2	7.5	47
		3	12.0	29
F	14.5	1	10.0	133
G	15.0	1	5.0	19
		2	4.5	54
		3	8.0	0
		4	3.5	31
H	15.2	1	7.0	42
		2	4.0	65
		3	14.0	0
		4	14.0	0
		5	7.5	52
I	6.4	1	12.5	0
		2	5.0	252
		3	4.5	187
J	14.1	1	13.0	0
		2	3.5	0
K	26.4	1	14.0	0
		2	4.0	0

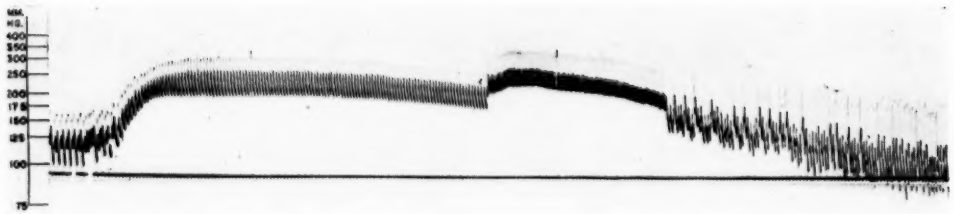

Fig. 1.—Blood pressure response to intravenous injection of 1.0 mg. epinephrine. Injection period indicated by interruptions of base line. Note the slow development of the primary rise in pressure associated with slowing of the heart rate, in contrast with the sudden onset of the secondary rise in blood pressures followed in a beat or two by the paroxysm of ventricular tachycardia. At the end of the paroxysm the pressure falls abruptly, and continues downward below control levels. After a variable period of five to fifteen minutes, the pressure returns to approximately control values (not shown). Calibration in mm. Hg shown at left. Time in seconds below.

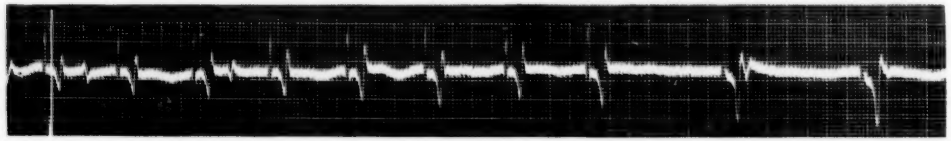

Fig. 2.—Electrocardiogram (Lead II) following the intravenous administration of 1.0 mg. of epinephrine showing a progressively increasing inhibition of the sinus node. The white line interrupting the curve deno es completion of the injection. The progressive increase in the P-P interval is clearly seen. The third auricular complex is followed by a five second interval of auricular standstill. The last P wave is merged with the T wave of the second to last beat. The P waves vary in contour. Complete A-V block began during the epinephrine injection. Idioventricular rhythm shifts to a new and slower pacemaker in the last two beats.

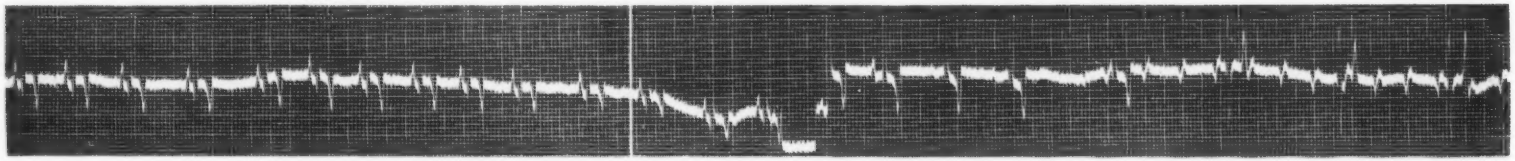

Fig. 3.—Electrocardiogram (Lead II) taken during and after the intravenous injection of 1.0 mg. of epinephrine. Prior to, and for several beats following, the termination of the injection (indicated by the white line) a sinus arrhythmia is present. This is followed by a shift in the sinus pacemaker which in turn is superseded by a sinus tachycardia (rate 158 to 170) with a differently contoured P wave, and complete A-V block with an idioventricular pacemaker which shifts in location (rate 52).

standstill (or S-A block) and nodal escapes (Fig. 5), and partial or complete A-V block (Figs. 2, 3, 4, and 6), gave way suddenly to a paroxysm of ventricular tachycardia (Fig. 7). This either was continuous or occurred in bursts (intermingled on occasion with single ventricular premature systoles), with a rate generally of about 200 to 220 beats per minute, although rates faster than this were encountered (Fig. 7). At this time the blood pressure showed a sharp secondary rise (Fig. 1). This rise sometimes preceded or coincided with the ventricular tachycardia. When the ventricular tachycardia was intermittent, it was interspersed with sinus or nodal tachycardia at a rate only slightly slower than the ventricular tachycardia. The ventricular tachycardia generally developed within 1 to 2 minutes, and persisted for from eleven seconds to five minutes. The animals often retched or vomited during this period. During the period of ventricular tachycardia, or just before, a marked tachypnea usually developed, with respiratory rates rising to about 300 per minute (Fig. 6). After cessation of the ventricular tachycardia a brief period of bradycardia, with or without the arrhythmias observed in the pretachycardia period, frequently occurred. This was soon replaced by a sinus tachycardia. In some instances the sinus tachycardia followed at once after the ventricular tachycardia.

Susceptibility to the occurrence of ventricular tachycardia appears to vary in different animals. This coincides with the experience of Meek and associates.[4] However, ventricular fibrillation was not induced in any of our animals. The susceptibility to ventricular tachycardia could not be related to the age or the sex of the dog, or to the slight variations in dose or rate of injection. Nevertheless, it is possible that larger dose or faster rates of injection might have increased the percentage of successful trials. Because of the rapid destruction it is apparent that the slow injection of epinephrine is equivalent in many respects to reduction in dosage.

The Effect of Atropine.—The intravenous administration of 1.3 mg. of atropine sulfate to seven of our trained unanesthetized dogs was followed within one minute by a sinus tachycardia (Fig. 8), the rate rising to about 250 to 290 per minute. Respiration became more rapid, the pupils dilated, and there was dryness of the oral mucosa.

The Inhibition of Ventricular Tachycardia by Atropine.—The results are given in Table II. One to five minutes following the administration of atropine, the administration of 1.0 mg. of epinephrine resulted in a rise in blood pressure and the heart rate increased to rates of about 300 per minute (Fig. 9). The reflex bradycardia after epinephrine previously seen was now absent. Retching and vomiting occurred. In only one out of nine trials in seven dogs was a run of ventricular tachycardia observed. In this exception, the dog, which was the largest in our series (and, therefore, received the smallest dosage per kilogram), exhibited a run of ventricular tachycardia which persisted for forty-four seconds.

As can be seen by comparing Tables I and II, each of the animals was tested to determine that it was capable of responding to the epinephrine by the appearance of ventricular tachycardia. All had given three positive control responses to epinephrine in the absence of atropine.

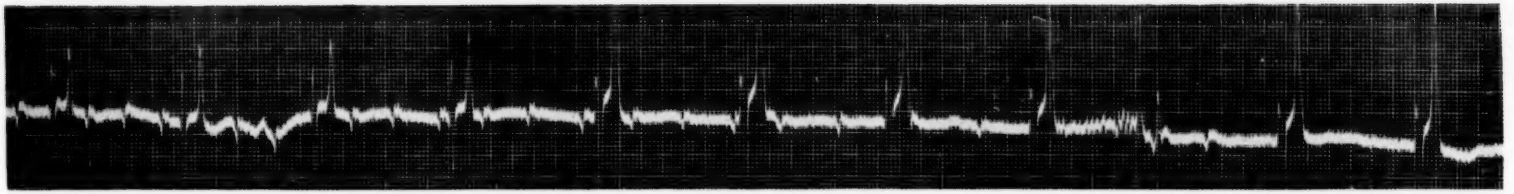

Fig. 4.—Electrocardiogram (Lead II) taken immediately after the administration of 1.0 mg. of epinephrine intravenously showing persistence of sinus tachycardia (rate 170) and complete A-V block (ventricular rate 48). Subsequent progressive slowing of the sinus pacemaker occurs with final disappearance of the P waves. This is associated with a shifting (and slowing) of the idioventricular pacemaker. The oscillations toward the end of the record are extracardiac artefacts.

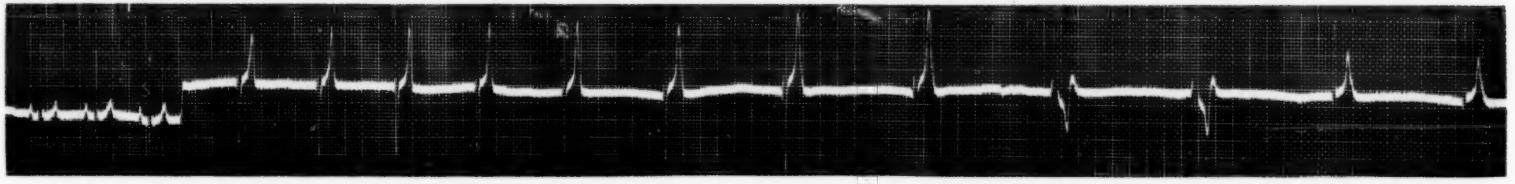

Fig. 5.—Electrocardiogram (Lead II) taken immediately after the intravenous injection of 1.0 mg. of epinephrine showing an abrupt arrest of the sinus node, followed by the assumption of pace maker function by an idioventricular pacemaker and progressive slowing of the latter. The site of the ventricular impulse formation varies.

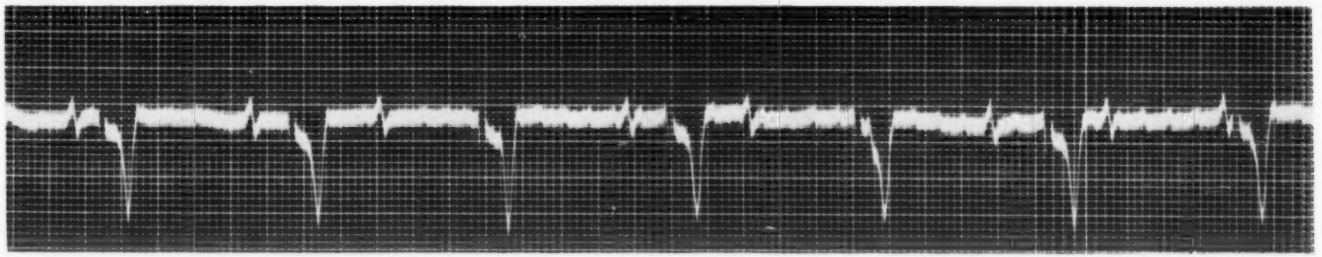

Fig. 6.—Electrocardiogram (Lead II) taken immediately after the intravenous injection of 1.0 mg. of epinephrine showing sinus arrhythmia and complete A-V block with an idioventricular pacemaker arising from one focus. The auricular rate averages 86, the ventricular rate, 57 per minute. In the second half of the curve are regularly spaced, very small upright deflections resembling P waves. Pneumographic records have shown these to represent the marked post-apneic tachypnea frequently observed after intravenous administration of epinephrine. Temporary slowing of the timer lines occurs in the last portions of the record.

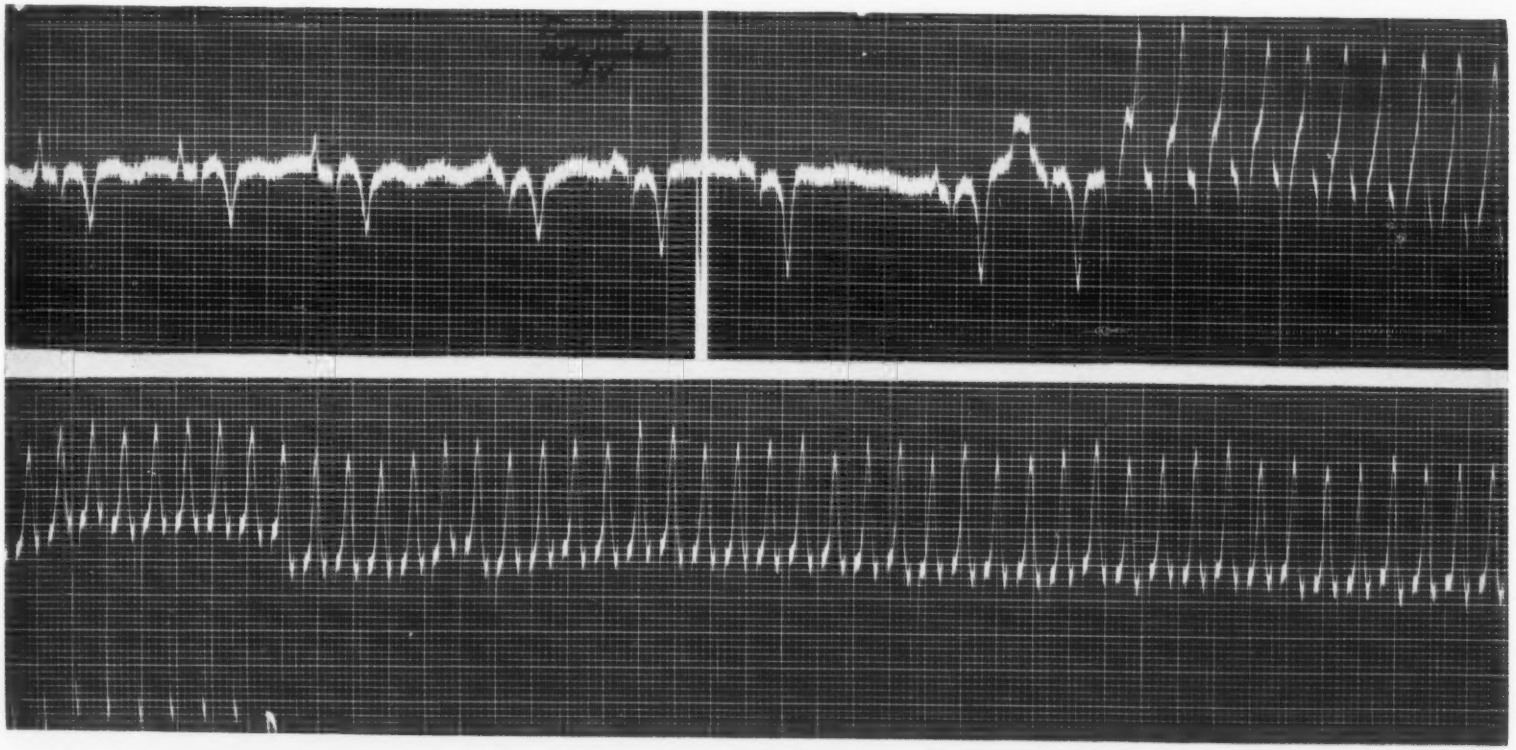

Fig. 7.—Electrocardiogram (Lead II) taken during and after the administration of 1.0 mg. epinephrine. The white line in the upper strip indicates the completion of the injection. Note the abrupt onset of ventricular tachycardia. The ventricular rate at the beginning of the paroxysm is 270 per minute. In the lower strip taken during the height of the paroxysm the rate is 330.

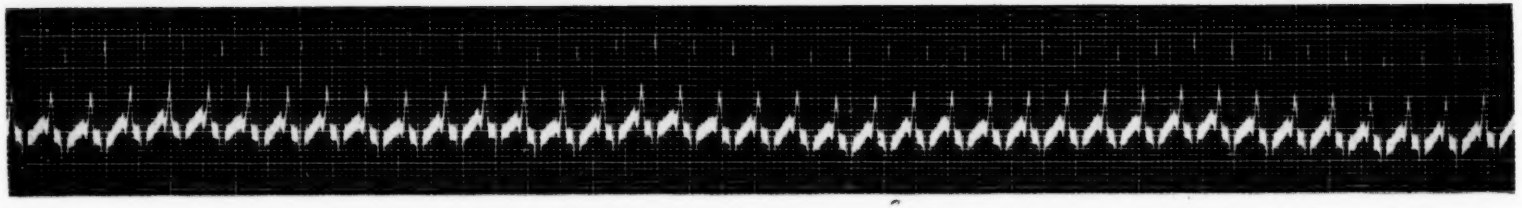

Fig. 8.—Electrocardiogram (Lead II) showing a sinus tachycardia with a rate of 270 per minute following the intravenous administration of 1.3 mg. of atropine.

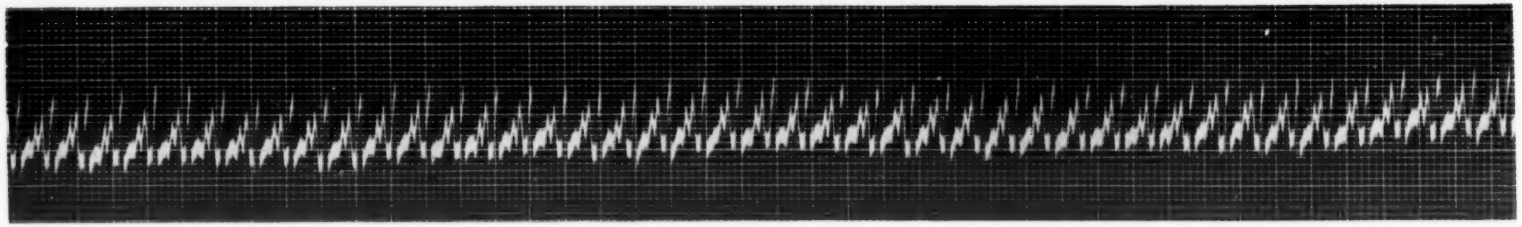

Fig. 9.—Electrocardiogram (Lead II) showing a sinus tachycardia with a rate of 300 per minute following the intravenous administration of 1.0 mg. of epinephrine to an atropinized dog (the same animal illustrated in Fig. 8). The prevention of ventricular tachycardia by the latter drug in this animal may result from retention of pacemaker function by the sinus node, since its rate of discharge is more rapid than that of the potential ventricular focus. This explanation does not apply to all animals.

TABLE II. EFFECT OF ATROPINE IN PREVENTING EPINEPHRINE-INDUCED PAROXYSMAL VENTRICULAR TACHYCARDIA

DOG	DURATION OF ATROPINE INJECTION (SEC.)	INTERVAL AFTER ATROPINE AT WHICH EPINEPHRINE WAS ADMINISTERED (SEC.)	DURATION OF EPINEPHRINE INJECTION (SEC.)	TOTAL DURATION OF PAROXYSMAL VENTRICULAR TACHYCARDIA (SEC.)
A	14.0	68	10.0	0
B	14.0	78	8.0	44
C	8.5	63	14.0	0
D	8.5	100	4.5	0
E	10.0	111	7.0	0
G	45.0	300	7.0	0
	5.5	100	4.0	0
H	15.0	300	15.0	0
	22.5	112	5.0	0

DISCUSSION

It is well known that epinephrine increases the rate of the isolated heart. This is not always seen in the intact unanesthetized animal. Instead, a slowing of the heart occurs due to a reflex from the carotid sinus and the aortic depressor mechanism acting over the vagi. Also, because of this moderator mechanism, the blood pressure rise is modified and reduced. If the dose of epinephrine is sufficient to overcome this moderator mechanism, at least for a time, the pressor and cardiac accelerating actions of epinephrine may lead to a sudden rise in pressure and heart rate to the levels which would have been obtained had it not been for the moderating secondary mechanisms. At this time the stimulation of ectopic pacemakers which epinephrine causes, combined with the depression of the sinus node, may permit the development of paroxysmal ventricular tachycardia.

Our observation that atropine tends to prevent experimentally induced paroxysmal ventricular tachycardia is in accord with previous observations (Petzetakis and Vlachlis, [1,10,11]) who found that atropinization prevented the occurrence of conduction disturbances induced by epinephrine in the rabbit. Seevers and associates[9] noted in dogs that atropine raised the level of cyclopropane concentration necessary to cause ectopic ventricular rhythm. Akita[2] recently reported that atropinization, bilateral vagotomy, or bilateral resection of the depressor nerves prevented the occurrence of epinephrine-induced ectopic ventricular rhythms in the rabbit. Hoff and Nahum[3] found vagotomy in cats lightly anesthetized with sodium amytal usually prevented epinephrine-induced ventricular rhythms. Shen[12] found that bilateral vagotomy and carotid sinus denervation gave protection against benzol-epinephrine-induced ventricular

fibrillation. However, Allen and associates[8] found that bilateral vagotomy did not abolish ventricular tachycardia induced by cyclopropane in fifteen out of nineteen cats. They also found in eight cats that atropine in doses of 0.02 to 0.2 mg. per kilogram subcutaneously also failed to prevent the ventricular arrhythmia.

Hoff and Nahum[3] attributed their results to a synergistic action of vagotomy and epinephrine in raising the rate of the sinus pacemaker to a level exceeding that of the potential rate of the ventricular ectopic pacemaker. This enhancement of the sinus rate keeps the ectopic pacemaker suppressed and prevents it from "escaping" and assuming control of the ventricles. In our experiments, also, four of six dogs showed a rate of the sinus node after atropine and epinephrine faster than that of the ventricular tachycardia induced by epinephrine alone (using the shortest cycles in the measurements). This tends to support the view of Hoff and Nahum.

This, however, need not be the mechanism involved. It may be that the ectopic ventricular rhythm is a vagus effect. It occurs in the midst of the vagal bradycardia and it is abolished by atropine at the same time as the bradycardia. In support of this view, the work of Otto and Gold[13] may be mentioned. They found in a patient predisposed to spontaneous supraventricular paroxysmal tachycardia that these attacks of rapid heart action could be induced by epinephrine. Atropine sulfate (4.0 mg. subcutaneously) administered over a period of twenty minutes could prevent the epinephrine-induced tachycardia. Under atropine, the sinus rate ranged from 106 to 132 per minute and yet the ectopic pacemaker, having a rate of 200 or more, was inhibited. The mechanism suggested by Hoff and Nahum[3] can not be invoked in such a case, nor can it be invoked in two of our six dogs in which the sinus rate after atropine and epinephrine was slower than that of the ventricular tachycardia induced by epinephrine alone.

The concept that epinephrine acts reflexly to produce both the bradycardia and ectopic rapid ventricular beating is supported indirectly by the signs of reflex or direct central nervous system stimulation in the form of tachypnea, retching, and vomiting which follow epinephrine administration. Recently, evidence has accumulated that chlorinated hydrocarbons, which also cause ventricular tachycardia, operate via the central nervous system and act through the acetylcholine esterase system.[14] It has been shown by Beattie, Brow, and Long[15,16] that direct stimulation of the hypothalamus may lead to the appearance of ventricular premature systoles. Atropine, by its effect on the acetylcholine esterase system, would interfere with such reflex cholinergic actions of epinephrine.

It has been shown by LeRoy, Fenn, and Gilbert[17] that atropine reduces the mortality rate from 70 per cent to 34 per cent in dogs anesthetized by morphine and nembutal, and to 50 per cent in unanesthetized dogs in which the anterior descending branch of the left coronary artery had been previously ligated. Death in all animals, whether atropinized or not, was due to ventricular fibrillation. Studies such as this have been the basis of the clinical use of atropine in recent myocardial infarction. From the results of our studies and those of others cited,

atropine would appear to act on the acetylcholine-cholinesterase mechanism to prevent reflex vagal-induced ventricular premature systoles, paroxysmal tachycardia, and fibrillation. The concept that atropine abolishes a vagal coronary vasoconstriction[17] is not supported by the work of this laboratory (Mintz and Kondo,[18] and Katz and Jochim[19]).

SUMMARY

1. The rapid intravenous injection of epinephrine provides a simple and effective method for the experimental production of ventricular tachycardia in the intact, unanesthetized animal.

2. Utilizing this procedure, it was found that 1.3 mg. of atropine sulphate administered intravenously prevented the development of ventricular tachycardia. Apparently this is due, on occasion, to the action of atropine in permitting the sinus node to discharge at a rate more rapid than that of the ventricular focus, the former, thereby, retaining its pacemaker function. Not all cases can be explained in this way, however. It would appear that atropine operates also on the acetylcholine esterase system to prevent reflex cholinergic actions of epinephrine.

3. Atropine would appear to be of value in preventing ventricular tachycardia and maintaining a sinus tachycardia. This is of particular importance in myocardial infarction where the evolution of recent ventricular tachycardia to fibrillation may be averted.

4. It is suggested that the recently observed beneficial effects of atropine in lowering mortality in experimental coronary artery ligation may be due in large part to its prevention of ventricular tachycardia and terminal ventricular fibrillation.

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LANATOSIDE C IN THE TREATMENT OF PERSISTENT PAROXYSMAL AURICULAR TACHYCARDIA

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IN THE majority of cases, paroxysmal auricular tachycardia is a relatively benign disease. Attacks usually terminate spontaneously, or respond readily to reflex vagal stimulation such as carotid sinus pressure, ocular pressure, traction of the tongue, Valsalva's or Müller's experiments, induction of emesis, change of position, and so forth. There are, however, occasional attacks which are resistant to conservative measures and persist over a prolonged period of time. Prolongation of the rapid heart action may cause the patient marked apprehension and discomfort and may lead to cardiac failure, especially in the presence of underlying cardiac disease or other illness. Cooke and White[1] report seven cases in which death occurred and was either directly or indirectly attributable to paroxysmal supraventricular tachycardia. Vascular collapse, acute pulmonary edema, congestive failure, renal failure, embolic phenomena, and angina may occur.[2-4] Central nervous system symptoms such as temporary blindness, vertigo, hemianopsia, blurring of vision, mental confusion, psychosis, convulsions, and coma have been reported.[2,5] Levine[6] states that hemiplegia and gangrene due to low pulse pressure and low cardiac output may result. Electrocardiograms simulating those of coronary thrombosis may be found after cessation of an attack of paroxysmal tachycardia.[7] Rapid conversion of the abnormal mechanism is, therefore, desirable in many cases and may occasionally be lifesaving.

A wide variety of drugs has been employed in the treatment of resistant paroxysmal auricular tachycardia. Mecholyl,[8,9] prostigmine,[10] physostigmine,[11] cinchona alkaloids,[12] cardiac glycosides,[13] magnesium sulfate,[14] calcium salts,[15] potassium salts,[16] metrazol,[17] ergot derivatives, and parathyroid hormone[6] have all been used successfully as therapeutic agents. Injection or surgical excision of the stellate ganglion[18,19] has also been reported to be effective. Many of the drugs have undesirable side effects and toxic reactions. Some are not without considerable danger. Some are not very effective and others have been inadequately studied or are without rationale.

The choice of agent depends upon the urgency of the episode and the toxicity of the drug, but in general the least toxic drug that can be effective should be employed. Speed of action is desirable, but consistency in achieving the desired

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result, absence of undesirable side effects, and wide margin of safety are likewise important. Within recent years, rapidly acting crystalline digitalis preparations have been employed with increasing frequency and with frequent success. Junet[20] treated seven cases of paroxysmal auricular tachycardia with lanatoside C intravenously without a failure. Fahr and La Due[21] treated five cases with the same preparation successfully. Schwab and Willis[22] used *Digitalis lanata* and *Digitalis purpurea* preparations parenterally in seven cases with but one failure.

This report deals with further experience in the treatment of resistant paroxysmal auricular tachycardia with lanatoside C* intravenously.

CASE MATERIAL

Thirteen patients with prolonged refractory paroxysmal auricular tachycardia were treated with lanatoside C intravenously. One patient was treated with digalen intravenously. Seventeen paroxysms occurred in this group of cases. There were eight women and six men in the group and the ages ranged from 6 to 69 years. Complete data are given in Table I.

Ten of the fourteen patients had organic disease in addition to paroxysmal tachycardia. One patient was in Addisonian crisis with atypical pneumonia. Three patients had hypertensive cardiovascular disease and two of these had diabetes mellitus as well. One patient had arteriosclerotic heart disease and diabetes mellitus and one had tuberculous pericarditis. In one case the rapid heart action occurred during ligation of a patent ductus arteriosus, and in another it occurred after thyroidectomy (toxic adenoma). There was one case of intestinal obstruction and one of compression fracture of the spine. Three patients had cardiogenic shock and four patients were judged to be in early cardiac failure.

The diagnosis was confirmed electrocardiographically in all cases but one. Electrocardiograms, likewise, were taken during cessation of the attack in all cases but one. Patients with auricular flutter or paroxysmal auricular fibrillation were not included in this study. In all instances the attacks were of prolonged duration and did not respond to repeated and varied attempts at reflex vagal stimulation. Those found to be refractory were given 0.8 mg. (4.0 c.c.) of lanatoside C intravenously.† If no satisfactory response occurred within thirty minutes to an hour, another 0.8 mg. was given intravenously. No other medication was employed to control the tachycardia prior to, nor in conjunction with, the lanatoside C.

RESULTS

In sixteen cases the paroxysmal tachycardia ceased abruptly within forty minutes after the administration of the first dose of digitalis glycoside intravenously. One patient, who developed tachycardia during operation for the removal of a toxic adenoma of the thyroid, did not respond immediately but was found to have a normal mechanism approximately twelve hours after therapy (Case 10,

*Lanatoside C was furnished by Sandoz Chemical Works, Inc., New York, N. Y., under the trade name of Cedilanid.

†One patient, 6 years old, was given only 0.4 mg. of lanatoside C.

Table I). The time of response, excluding the case with delayed response, varied from four minutes to forty minutes and the average response was 17.6 minutes.

Ten patients responded to a dose of 0.8 mg. of lanatoside C, four patients to 1.6 mg., one patient to 1.0 mg., and one patient to 0.4 milligram. There were no toxic reactions nor undesirable side effects. The three instances of cardiogenic shock cleared up without further therapy.

Marked subjective and objective improvement occurred immediately in all cases upon cessation of the tachycardia. There was no immediate recurrence of the tachycardia. In those patients with organic disease the episode of tachycardia in no way affected the clinical course nor prolonged the hospital stay.

Five patients received carotid sinus pressure at varying intervals after the administration of the lanatoside C and in each case the paroxysm abruptly ceased, although repeated application of carotid sinus pressure previous to the injection of lanatoside C was ineffective. The remaining patients spontaneously reverted to a normal mechanism after therapy was instituted.

DISCUSSION

It is quite probable that the majority of these cases would have reverted to a normal mechanism without therapy. However, the desirability and necessity of rapid termination of the paroxysm in the patients is quite evident. It is entirely possible that the patient with Addisonian crisis, as well as those patients with underlying cardiovascular disease or cardiogenic shock, might have suffered serious complications or might have succumbed if the tachycardia had not been terminated rapidly. The alleviation of the patients' subjective distress was rapid and gratifying.

Carotid sinus pressure was ineffective prior to the institution of therapy in every case. However, five patients rapidly reverted to a normal mechanism when carotid sinus pressure was again attempted after lanatoside C was administered. Whether the response was due to the additive effect of the reflex vagal stimulation occurring with digitalization, or to increase in carotid sinus sensitivity, or to some other mechanism cannot be stated. It is possible that reapplication of carotid sinus pressure might have been successful without digitalis, but the uniform response in the face of previous failure makes this unlikely.

It is noteworthy that in this group of patients with resistant paroxysmal auricular tachycardia, ten of the fourteen, or 71.4 per cent, had associated organic disease. Marked delay in response occurred only in the patient with thyrotoxicosis. There was no correlation between the type and severity of the associated organic disease and the rapidity of response. The response of patients with uncomplicated paroxysmal tachycardia was no quicker than that of the remainder of the group.

Several patients with paroxysmal auricular flutter and paroxysmal auricular fibrillation were treated in an identical manner with lanatoside C while this series of cases was being collected. In these cases too, a rapid reduction in the ventricular rate occurred in every case and frequently a rapid reversion to normal

TABLE I. RESULTS OF LANATOSIDE C IN FOURTEEN PATIENTS WITH AURICULAR PAROXYSMAL TACHYCARDIA

CASE NO.	NAME	AGE	SEX	DIAGNOSIS	INITIAL HEART RATE	HEART RATE AFTER TREATMENT	MGM. LANATOSIDE C	TIME OF RESPONSE
1	A. G. #142–067	36	M	Primary atypical pneumonia; Addisonian crisis; paroxysmal nodal tachycardia	155	108	0.8	10 min.
2	E. J. #234–601	24	M	Tuberculous pericarditis and myocarditis; paroxysmal auricular tachycardia	190	120	1.6	40 min.
3	M. L.	45	F	Paroxysmal auricular tachycardia	200	90	0.8	8 min.
4	I. D. #237–539	58	M	Intestinal obstruction; peritoneal abscess; paroxysmal auricular tachycardia	225	130	0.8*	12 min.
5	M. M. #164–047	36	F	Paroxysmal auticular tachycardia	180	84	0.8*	15 min.
				Paroxysmal auricular tachycardia	240	86	0.8*	9 min.
6	J. L. #246–711	6	M	Ligation of patent ductus arteriosus; paroxysmal auricular tachycardia during procedure	195	134	0.4	35 min.
7	B. S. #246–738	54	F	Compression fracture of spine; obesity; paroxysmal auricular tachycardia	160	98	1.6*	40 min.
8	H. S. #228–032	55	F	Hypertensive cardiovascular disease; diabetes mellitus; carcinomatosis; paroxysmal auricular tachycardia	214	94	0.8	5 min.

9	A. S. #140–657	66	F	Diabetes mellitus; arteriosclerotic heart disease; cardiac decompensation; shock; paroxysmal auricular tachycardia	187	97	0.8	4 min.
				Diabetes mellitus; arteriosclerotic heart disease; paroxysmal auricular tachycardia	217	88	0.8*	6 min.
10	A. R. #254–094	46	F	Toxic adenoma of the thyroid; paroxysmal auricular tachycardia, postoperatively	220	84	1.6	12 hours, approx.
11	E. M. #120–847	48	F	Paroxysmal auricular tachycardia	183	75	1.0	30 min.
12	J. S.	23	M	Paroxysmal auricular tachycardia	170	90	0.8	15 min.
13	E. S. #202–267	54	M	Hypertensive cardiovascular disease; diabetes mellitus; shock; paroxysmal auricular tachycardia with transient left bundle branch block	208	100	0.8	6 min.
				Same diagnosis as above; shock; paroxysmal auricular tachycardia (no bundle branch block)	140	96	1.6	36 min.
14	M. B. HC–4643	53	F	Hypertensive cardiovascular disease; paroxysmal nodal tachycardia	188	94	6.0 c.c. digalen	10 min.

*Carotid sinus pressure reapplied.

sinus rhythm was observed. These patients were not included in this group of cases.

The uniformity of response, the rapidity of action, and the absence of toxicity or undesirable side effects makes lanatoside C a valuable therapeutic agent in the treatment of paroxysmal auricular tachycardia which does not respond to reflex vagal stimulation. It should be re-emphasized that drug therapy need not be employed unless reflex vagal stimulation is unsuccessful.

SUMMARY AND CONCLUSIONS

1. Sixteen patients with persistent paroxysmal auricular tachycardia were treated with lanatoside C intravenously. One patient was treated with digalen intravenously.

2. In sixteen cases the paroxysmal tachycardia abruptly ceased within forty minutes. The average time of response in these fifteen cases was 17.6 minutes. In one case the response occurred within twelve hours.

3. No toxic reactions nor undesirable side effects occurred.

4. Lanatoside C is a safe and effective agent in the therapy of paroxysmal auricular tachycardia which does not respond to reflex vagal stimulation.

We wish to express our appreciation to Miss Marjorie Frasier for her technical assistance.

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AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

V. The Effect of Changing Heart Rate Upon the Q-T Interval and the T-P Interval and Their Respective Relationships to the Cycle Length (R-R Interval)

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OF INTEREST to many investigators has been the question of determining exactly what happens to the Q-T interval, the T-P interval, and the cycle length (C) as measured in the electrocardiogram while the heart rate is changing. Lombard and Cope,[1] measuring systole and diastole by mechanical means, found that diastole shortened more rapidly than systole with increase in heart rate. Bazett[2] found that the ratio $K = \frac{Q\text{-}T}{\sqrt{C}}$ was temporarily increased immediately after exercise. White and Mudd[3] found that the Q-T to C relationship was not altered after exercise. Blair, Wedd, and Young[4] noted that immediately after exercise the Q-T and C were shorter than before exercise and that, as the C returned to the resting level, the Q-T lengthened, although at a slower rate, until it too had reached the resting level. However, the Q-T continued for a time to lengthen beyond that level while C remained constant. White, Kossmann, and Ershler[5] in their study found that the ratio $\frac{Q\text{-}T}{\sqrt{C}}$ became smaller immediately after exercise. In two previous reports[6,7] it was shown that the Q-T to C and T-P to C relationships [K(Q-T) and K(T-P)] were not disturbed immediately after exercise, but no information was available as to what happened while the heart rate was changing. It was for the purpose of obtaining information about this phase that this study was undertaken.

METHOD

The procedure followed was the same as that outlined in the study reported previously[8] with the following modifications. Only fifty-two of the fifty-three normal young men were retained for this study. Electrocardiograms were taken while the subject was seated in a comfortable straight-backed chair with his right foot resting on a pedal. The pedal was a board attached to the floor at one

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end by hinges and to a weight by means of rope and pulley at the other end. Stops were so placed that the distal (weighted) end of the board could traverse a distance of about six inches. The work performed in lifting the weight with the pedal was enough to induce a tachycardia. Thus, we were able to record the electrocardiograms during exercise. In each case the three standard limb leads were recorded at rest after the heart rate had become stabilized. Then, Lead II was recorded during ten of every fifteen seconds, or, in some cases, continuously while the subject exercised. When a tachycardia had been produced, exercise was stopped and tracings (Lead II) continued to be recorded until the heart rate had returned to the resting level and remained there for two minutes. In each individual the cycle length, Q-T interval, and T-P interval were measured and recorded for the different heart rates. The criteria used in selecting and measuring the cycles and intervals have been outlined previously.[6-8] Table I shows the age distribution of the fifty-two subjects retained for this study.

TABLE I. AGE DISTRIBUTION OF TOTAL NUMBER OF CASES

AGE (YR.)	NUMBER
19	2
20	5
21	12
22	17
23	11
24	3
25	0
26	1
27	0
28	0
29	0
30	1
Total	52

RESULTS AND DISCUSSION

In analyzing the data, it was found that the period from the beginning to the completion of the experiment in each instance could be divided into three stages as follows: (1) the stage during which the heart rate increases (cycle length becomes shorter), (2) the stage when the heart rate decreases (cycle length lengthens), and (3) the stage at which the heart rate has returned to the control level. Since the rates of change of the heart rate (and cycle length) and Q-T and T-P intervals vary so much from individual to individual, it was found to be impractical to draw a composite set of curves for the entire group. Therefore, only a few characteristic curves are illustrated in Fig. 1.

Examination of the curves reveals that during the first stage the K(Q-T) values become larger with shortening of the cycle length. During the second stage the K(Q-T) values become smaller than the control values. Finally, the K(Q-T) values reach a level that is the same as or close to the pre-exercise levels when the cycle length has returned to its resting level. At one point between

the first and second stages the K(Q-T) values are the same as those of the pre-exercise period. To help analyze the data further, the largest K(Q-T) value ["peak" K(Q-T)], as well as the mean of all the K(Q-T) values ["mean" K(Q-T)] during the first stage, was determined in each case (Table II). The mean of the "peak" K(Q-T) and the mean of the "mean" K(Q-T) were determined, and their deviations from the mean of the control K(Q-T) values were tested for

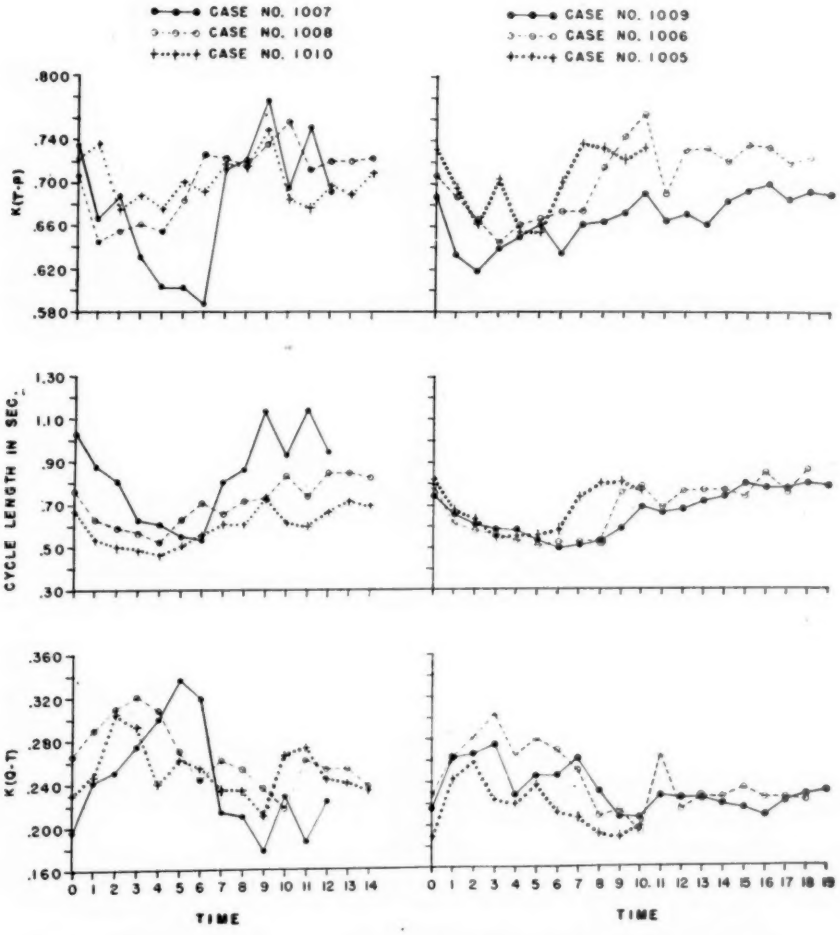

Fig. 1.—The effect of changing cycle length on K(Q-T) and K(T-P) as illustrated in six normal young men.

significance. It was found that the mean of the control K(Q-T) values was 0.237, with a standard deviation of ±0.021. The mean of the "peak" K(Q-T) was 0.293, with a standard deviation of ±0.029. The *t* value for the difference between the mean of the control K(Q-T) and the mean of the "peak" K(Q-T) was found to be 11.436. The *t* value for the difference between the mean of the control K(Q-T) and the mean of the "mean" K(Q-T) was found to be 7.734.

TABLE II. PEAK AND MEAN VALUES FOR K(Q-T) DURING PERIOD OF INCREASING HEART RATE

NO.	CASE	CONTROL K(Q-T)	PEAK K(Q-T)	MEAN K(Q-T)
1	1002	.230	.309	.284
2	1003	.246	.273	.255
3	1004	.281	.295	.287
4	1005	.190	.259	.242
5	1006	.230	.304	.279
6	1007	.197	.327	.286
7	1008	.267	.321	.307
8	1009	.219	.276	.254
9	1010	.230	.306	.271
10	1011	.219	.289	.252
11	1012	.249	.296	.263
12	1013	.251	.296	.271
13	1014	.262	.290	.266
14	1015	.187	.270	.252
15	1016	.220	.277	.273
16	1017	.285	.346	.258
17	1018	.231	.308	.292
18	1020	.221	.302	.268
19	1021	.247	.320	.281
20	1022	.222	.296	.276
21	1023	.250	.333	.291
22	1024	.224	.243	.243
23	1025	.236	.264	.217
24	1026	.233	.260	.228
25	1027	.254	.284	.277
26	1028	.209	.294	.263
27	1029	.233	.240	.232
28	1030	.241	.327	.302
29	1031	.204	.212	.211
30	1032	.256	.281	.281
31	1033	.244	.284	.267
32	1034	.229	.291	.259
33	1035	.270	.271	.271
34	1036	.216	.258	.257
35	1037	.263	.273	.246
36	1038	.245	.327	.321
37	1039	.241	.286	.283
38	1040	.261	.333	.295
39	1041	.235	.323	.282
40	1042	.262	.298	.292
41	1044	.244	.259	.240
42	1045	.247	.267	.237
43	1047	.245	.292	.275
44	1048	.221	.266	.259
45	1049	.250	.333	.280
46	1050	.217	.300	.267
47	1051	.213	.323	.294
48	1052	.240	.355	.289
49	1053	.245	.318	.298
50	1054	.248	.273	.265
51	1055	.228	.306	.302
52	1056	.244	.278	.278
Mean K(Q-T)		0.237	0.293	0.270
Standard deviation		±0.021	±0.029	±0.023

Comparison of "Peak" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.004897$$

$$t = \frac{\overline{X}_1 - \overline{X}_2}{sd} = \frac{0.056}{0.004897} = 11.436$$

$\overline{X}_1$ = Mean of "peak" K(Q-T)

$\overline{X}_2$ = Mean of control K(Q-T)

Comparison of "Mean" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.004267$$

$$t = \frac{\overline{X}_1 - \overline{X}_2}{sd} = \frac{0.033}{0.004267} = 7.734$$

$\overline{X}_1$ = Mean of "mean" K(Q-T)

$\overline{X}_2$ = Mean of control (K(Q-T)

Thus, it is seen that the deviations of K(Q-T) which occur during the first stage are highly significant. The second stage was analyzed similarly (Table III). The difference between the mean of the "mean" K(Q-T) and the mean of the control K(Q-T) was found to be not statistically significant. However, the mean of the "peak" K(Q-T) differed from the mean of the control K(Q-T) significantly. It is therefore seen that the K(Q-T) value becomes significantly greater during the first stage, whereas during the second stage only isolated readings of K(Q-T) are significantly smaller than the K(Q-T) value during the control period. From this data and from perusal of the individual Q-T and C values in each case it is seen that the rate of change of the Q-T interval lags slightly behind the rate of change of the cycle length during changing heart rate. However, the direction of change is the same for both.

In Fig. 1 it is seen that with the shortening of the cycle length the value of K(T-P) becomes smaller during the first stage. During the second stage the value of K(T-P) becomes greater and surpasses the control value. Finally, K(T-P) assumes the control value during the third stage. At one point between the first and second stages the value of K(T-P) is the same as that of the pre-exercise period. In Table IV are listed the "peak" K(T-P) (that is, the smallest value of K(T-P) during the first stage), as well as the "mean" K(T-P) (that is, the mean of all K(T-P) values during the first stage), for each subject. Upon determining their respective means and testing the significance of their deviations from the mean of the control K(T-P), it is seen that the difference between the mean of the "peak" K(T-P) and the mean of the control K(T-P), as well as the difference of the mean of the "mean" K(T-P) from the mean of the control K(T-P), is statistically significant. The data obtained during the second stage was similarly analyzed and, as is seen in Table V, only the difference between the mean of the "peak" K(T-P) and mean of the control K(T-P) was statistically significant. The mean of the "mean" K(T-P) did not differ significantly from the control value. It is seen, therefore, that during the first stage there is a significant de-

TABLE III. PEAK AND MEAN VALUES FOR K(Q-T) DURING PERIOD OF DECREASING HEART RATE

NO.	CASE	PEAK K(Q-T)	MEAN K(Q-T)
1	1002	.211	.244
2	1003	.226	.245
3	1004	.236	.257
4	1005	.207	.219
5	1006	.194	.231
6	1007	.178	.201
7	1008	.218	.248
8	1009	.207	.227
9	1010	.210	.239
10	1011	.202	.216
11	1012	.206	.243
12	1013	.214	.248
13	1014	.220	.235
14	1015	.178	.215
15	1016	.199	.224
16	1017	.279	.305
17	1018	.213	.241
18	1020	.196	.222
19	1021	.177	.228
20	1022	.208	.234
21	1023	.222	.261
22	1024	.208	.224
23	1025	.208	.254
24	1026	.199	.226
25	1027	.217	.253
26	1028	.199	.229
27	1029	.225	.232
28	1030	.218	.268
29	1031	.203	.207
30	1032	.191	.259
31	1033	.214	.244
32	1034	.212	.213
33	1035	.220	.254
34	1036	.197	.229
35	1037	.217	.242
36	1038	.235	.257
37	1039	.244	.258
38	1040	.240	.271
39	1041	.196	.224
40	1042	.197	.233
41	1044	.209	.248
42	1045	.181	.218
43	1047	.203	.240
44	1048	.181	.208
45	1049	.218	.249
46	1050	.176	.203
47	1051	.237	.271
48	1052	.179	.229
49	1053	.199	.236
50	1054	.238	.254
51	1055	.205	.246
52	1056	.204	.216
Mean K(Q-T)		0.209	0.238
Standard deviation		±0.020	±0.020

Comparison of "Peak" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.003966$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.028}{0.003966} = 7.060$$

$\bar{X}_1$ = Mean of control K(Q-T)

$\bar{X}_2$ = Mean of "peak" K(Q-T)

Comparison of "Mean" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00398$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.001}{0.00398} = 0.252$$

$\bar{X}_1$ = Mean of "mean" K(Q-T)

$\bar{X}_2$ = Mean of control K(Q-T)

crease in the value of K(T-P), whereas during the second stage only isolated readings may be significantly greater than the control K(T-P). These data plus a perusal of the individual T-P and C values in each case show that, although the direction of change is the same in both C and T-P, the rate of change in T-P is greater than the rate of change in the cycle length.

On the basis of this work it is felt that a constant relationship between Q-T and C and between T-P and C holds in normal young men only when the heart rate is stable. Whenever this stability is upset and the heart rate is changing, the relationships are distrubed. In two previous reports[6,7] it was shown that the relationships K(Q-T) and K(T-P) were not disturbed immediately after exercise. In reviewing this previous data and method in the light of our present experience it is felt that the reason no disturbance of the K(Q-T) and K(T-P) relationships was found immediately after exercise was that practically all of the afterexercise tracings were recorded during the short transition period between the first and second stages when the K(Q-T) and K(T-P) values are practically the same as those of the pre-exercise period. It is conceivable that a slight delay in recording the afterexercise tracings might have placed us in the middle of the second stage; but, even if all of the after exercise tracings had been recorded during the second stage, our conclusion might have been the same, for, as was shown in the foregoing, the deviations of the means of all the "mean" K(Q-T) and the "mean" K(T-P) from their respective control means are not statistically significant. It is only the extreme K(Q-T) and K(T-P) values that deviate significantly, and unless continuous tracings were taken, the likelihood is that the scatter of the K(Q-T) and K(T-P) values for the entire group would be such as to give us a set of means that did not deviate significantly from the control values.

TABLE IV. PEAK AND MEAN VALUES FOR K (T-P) DURING PERIOD OF INCREASING HEART RATE

NO.	CASE	CONTROL K(T-P)	PEAK K(T-P)	MEAN K(T-P)
1	1002	.687	.566	.609
2	1003	.644	.630	.657
3	1004	.660	.640	.657
4	1005	.732	.662	.688
5	1006	.708	.644	.666
6	1007	.735	.587	.629
7	1008	.707	.646	.655
8	1009	.686	.618	.639
9	1010	.722	.674	.693
10	1011	.694	.598	.657
11	1012	.672	.613	.676
12	1013	.622	.576	.595
13	1014	.671	.639	.654
14	1015	.714	.667	.686
15	1016	.728	.662	.667
16	1017	.685	.634	.723
17	1018	.690	.612	.617
18	1020	.714	.661	.677
19	1021	.712	.643	.668
20	1022	.720	.631	.653
21	1023	.661	.578	.626
22	1024	.711	.678	.678
23	1025	.699	.684	.722
24	1026	.678	.685	.705
25	1027	.694	.662	.680
26	1028	.688	.566	.605
27	1029	.657	.660	.686
28	1030	.691	.622	.659
29	1031	.748	.723	.732
30	1032	.688	.702	.702
31	1033	.680	.657	.673
32	1034	.706	.620	.657
33	1035	.683	.688	.688
34	1036	.728	.667	.670
35	1037	.675	.660	.674
36	1038	.691	.605	.609
37	1039	.679	.624	.630
38	1040	.671	.584	.633
39	1041	.666	.561	.597
40	1042	.682	.616	.644
41	1044	.646	.614	.672
42	1045	.681	.667	.708
43	1047	.683	.612	.638
44	1048	.700	.651	.662
45	1049	.691	.589	.643
46	1050	.716	.643	.659
47	1051	.731	.590	.627
48	1052	.770	.544	.633
49	1053	.686	.616	.633
50	1054	.713	.681	.693
51	1055	.721	.612	.626
52	1056	.692	.649	.649
Mean K(T-P)		0.694	0.633	0.659
Standard deviation		±0.027	±0.039	±0.032

Comparison of "Peak" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00662$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.061}{0.00662} = 9.215$$

$\bar{X}_1$ = Mean of control K(T-P)
$\bar{X}_2$ = Mean of "peak" K(T-P)

Comparison of "Mean" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00587$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.035}{0.00587} = 5.963$$

$\bar{X}_1$ = Mean of control K(T-P)
$\bar{X}_2$ = Mean of "mean" K(T-P)

Since changing heart rate disturbs the K(Q-T) and K(T-P) ratios, it is important to note whether or not the heart rate was stable in all instances where these relationships or even where only the Q-T interval is being studied. Unless the heart rate was known to be stable at the time the tracings were recorded there is no basis for comparing the values for K(Q-T), K(T-P), or Q-T with the "normal" or "control" values. This is expecially true in acute experiments where the heart rate is disturbed by such factors, for example, as induced anoxia, hyperthermia, effects of short-acting drugs such as epinephrine, etc., and emotional factors. This must also be kept in mind when studying the tracings of young individuals, for sinus arrhythmia is a common finding among these persons.

CONCLUSIONS

1. In normal young men the Q-T interval to cycle length relationship is disturbed during changing heart rate produced by exercise. The K(Q-T) becomes larger during the period of increasing heart rate and hovers around the control level with wide fluctuations toward smaller values during the period of decreasing heart rate. This is due to the fact that the rate of change of Q-T is slower than the rate of change of the cycle length.

2. In normal young men the T-P interval to cycle length relationship is disturbed during changing heart rate produced by exercise. The K(T-P) becomes smaller during the period of increasing heart rate and hovers around the control level with wide fluctuations toward larger values during the period of decreasing heart rate. This is due to the fact that the rate of change of T-P is greater than the rate of change of the cycle length.

TABLE V. PEAK AND MEAN VALUES FOR K(T-P) DURING PERIOD OF DECREASING HEART RATE.

NO.	CASE.	PEAK K(T-P)	MEAN K(T-P)
1	1002	.718	.669
2	1003	.690	.673
3	1004	.706	.697
4	1005	.739	.688
5	1006	.768	.715
6	1007	.778	.737
7	1008	.758	.724
8	1009	.691	.670
9	1010	.749	.714
10	1011	.708	.689
11	1012	.746	.698
12	1013	.641	.616
13	1014	.704	.692
14	1015	.780	.729
15	1016	.758	.727
16	1017	.705	.677
17	1018	.729	.694
18	1020	.742	.714
19	1021	.799	.735
20	1022	.739	.697
21	1023	.706	.657
22	1024	.723	.702
23	1025	.735	.679
24	1026	.760	.726
25	1027	.727	.687
26	1028	.704	.663
27	1029	.690	.677
28	1030	.667	.660
29	1031	.749	.732
30	1032	.778	.691
31	1033	.741	.700
32	1034	.736	.727
33	1035	.712	.689
34	1036	.747	.707
35	1037	.712	.696
36	1038	.701	.682
37	1039	.692	.671
38	1040	.704	.667
39	1041	.717	.675
40	1042	.771	.720
41	1044	.696	.663
42	1045	.767	.733
43	1047	.763	.705
44	1048	.716	.708
45	1049	.732	.685
46	1050	.766	.727
47	1051	.708	.658
48	1052	.756	.691
49	1053	.758	.709
50	1054	.709	.685
51	1055	.744	.694
52	1056	.729	.715
Mean K(T-P)		0.730	0.695
Standard deviation		±0.031	±0.025

Comparison of "Peak" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00579$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.036}{0.00579} = 6.218$$

$\bar{X}_1$ = mean of peak K(T-P)
$\bar{X}_2$ = Mean of control K(T-P)

Comparison of "Mean" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00516$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.001}{0.00516} = 0.194$$

$\bar{X}_1$ = Mean of "mean" K(T-P)
$\bar{X}_2$ = Mean of control K(T-P)

3. The importance of these disturbances in the K(Q-T) and K(T-P) ratios and their influence in certain circumstances are discussed.

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Clinical Reports

PAROXYSMAL DIAPHRAGMATIC FLUTTER WITH SYMPTOMS SUGGESTING CORONARY THROMBOSIS

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FROM time to time, since 1936, reports have appeared in the literature concerning a nomadic individual of various aliases, who presents the unusual association of recurring attacks of diaphragmatic flutter, symptoms suggestive of coronary thrombosis, and psychopathic prevarication. Porter[1] of Virginia first described the temporary relief of severe anginal pain in this patient by procaine infiltration of each phrenic nerve, after kymography and fluoroscopy had revealed the presence of diaphragmatic flutter. In his description of the syndrome he concluded that the term "cardiodiaphragmatic angina" was justified. In 1939, Whitehead and associates[2] of Colorado University published extensive observations on the same patient; during his hospital stay a left phrenicotomy and a right phrenic crush were done to arrest the episode of diaphragmatic flutter, with evident temporary success and relief of precordial pain. An additional communication concerning this individual was included in the same article, in the form of observations by Lagen and others at the University of California Hospital on this patient a year later. At that time, left phrenic exeresis (31 cm.) and right phrenicotomy were done by the California group with relief of the flutter episode and of the anginal pain. During this latter period of observation evidence of hysterical or feigned hemiplegia were recorded; frequently elevated temperature was thought due to malingering. In 1941, Goodman[3] of Oregon University reported temporary relief of anginal pain and flutter of the diaphragm in the same man by ethyl chloride refrigeration over the phrenics, and suggested this procedure for further trial in other forms of disturbed diaphragmatic motility. The last communication concerning the patient was submitted by Caine and Ware,[4] who in 1944 treated him in an Army hospital for the same condition, the paroxysms of flutter, pain, and dyspnea finally ceasing after treatment with bed rest, morphine, and oxygen. In addition to the published reports just cited, it is known that this same patient has been seen and treated for his fluttering diaphragm and angina in at least six other institutions, mostly on the Pacific coast. In each instance house staffs have been intrigued

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by the various callings and pursuits alleged by the subject, and the saga of his life as related in various hospitals has revealed him as a deep sea diver, a miner, trapper, sheriff, and retired Army officer. In nearly all instances, evidences of psychopathy also have included malingering or belligerency. Identification has been possible by means of pictures, scars, and tatoo marks, as well as by means of the association of complaints. The observations here submitted confirm previous ones, and attempt to add further to the clinical picture of the attack as seen.

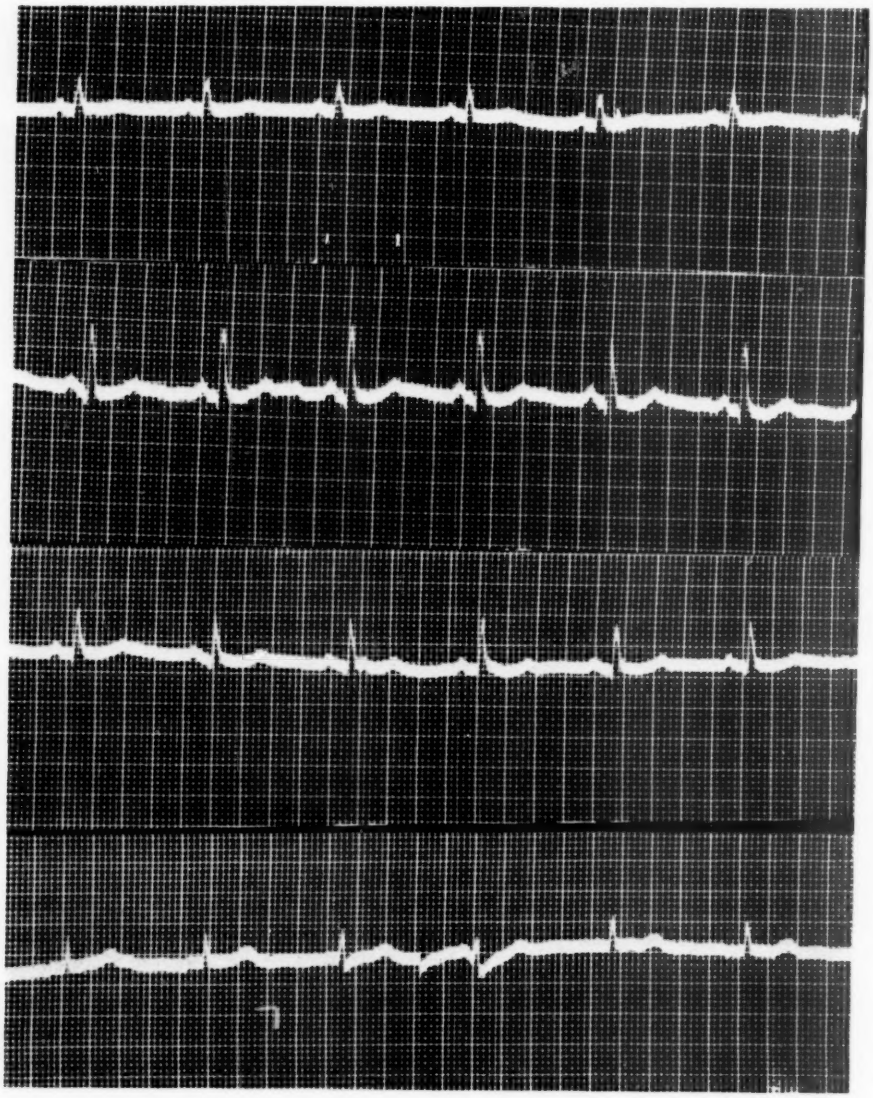

Fig. 1.—Electrocardiogram taken during the height of a paroxysm of diaphragmatic flutter.

CASE REPORT

On Aug. 14, 1946, a man was brought by the police to the emergency room of Palo Alto Hospital, stating that he had been seized by severe chest pain and had collapsed while getting off a bus. He gave the name of "Lewis Allen", was dressed in khaki enlisted men's clothing and Army garrison cap, and complained bitterly of agonizing precordial pain, clutching his left breast, moaning, and gritting his teeth. Examination revealed a thin, undernourished man around 60 years of age, with thin gray-brown hair; the eyes were light brown, with small but normally reacting pupils. Marked septal deviation occluded the right nostril, and complete dentures were present. A diagonal white scar traversed the central portion of the lower lip. On each side of the neck old transverse scars 5 cm. in length were present a short distance above the clavicle, just lateral to the sternomastoid insertions. An eagle was tatooed on the right forearm, and a wreath of flowers on the left. On auscultation over the precordium a loud rapid booming sound was heard, about 240 per minute in frequency, in the presence of a pulse rate of 72 at the wrist. Palpation over the lower thorax both back and front, conveyed a marked throbbing sensation to the hand synchronous with the sounds described. The blood pressure was 90/60. Physical examination was otherwise not remarkable.

Because of the bitter complaints of "pain in my heart" a tentative diagnosis of coronary thrombosis was made, and morphine sulphate, ¼ grain, was given hypodermically. Following this, an electrocardiogram was run (Fig. 1) which revealed a sinus rhythm with a rate of 70, and no changes suggestive of either coronary insufficienty or of infarction. At this juncture, the similarity existing between the patient and the one described in the literature occurred to us, and he was placed under the fluoroscope. Here both leaves of the diaphragm were seen to be fluttering rapidly in time with the palpable impulses and audible sounds previously noted. The excursion of the leaves was estimated as between 5 and 10 mm., and seemed slightly more marked on the right side. The left leaf of the diaphragm was elevated to the level of the fifth rib, with slight shift of the cardiac shadow to the right (Fig. 2).

The patient continued to cry out with distress and evince all signs of severe pain despite the hypodermically administered morphine. A second dose of 1/8 grain was given, this time by vein, slowly, and with relief of pain. The flutter, however, was not stopped, but was noted to assume a more irregular rhythm at a somewhat slower rate, disappearing spontaneously several hours later not to recur. A routine complete blood count was within normal limits, and the Kolmer was negative. A six-foot roentgenogram of the chest (Fig. 2) merely confirmed previous fluoroscopic observations of cardiodiaphragmatic relations. A recheck electrocardiogram on the following day failed to show any interim changes.

On further conversation with the patient, he stated that he was a retired Navy ensign, recently released from Santo Tomas internment camp in the Philippines, where he stated that he had been imprisoned by the Japanese since 1941. The scar on his lower lip, he explained, was due to a Japanese sniper's bullet, and the scars at the base of his neck were due to old operations "for tuberculosis." He also stated that he had served as a "radar installer" in the amphibious assaults on Tarawa, Saipan, Iwo Jima, and Okinawa, which seem to constitute a temporal paradox worthy of note. On being questioned as to previous attacks of chest pain or flutter of the diaphragm, and previous hospital admissions, he denied any such incidents but was quick to refuse us permission to photograph him. The next day after admission he stated that he felt fine and desired to go to a nearby city for his pension check. This he was allowed to do, since the need of hospital beds was urgent at the time.

COMMENT

In view of the extensive phrenic interruptions carried out on this man, particularly in regard to the left nerve and left leaf of the diaphragm, it is felt that the episodes of flutter may at present be due either to the presence of accessory phrenic pathways, or to a myogenic tic of the diaphragm.

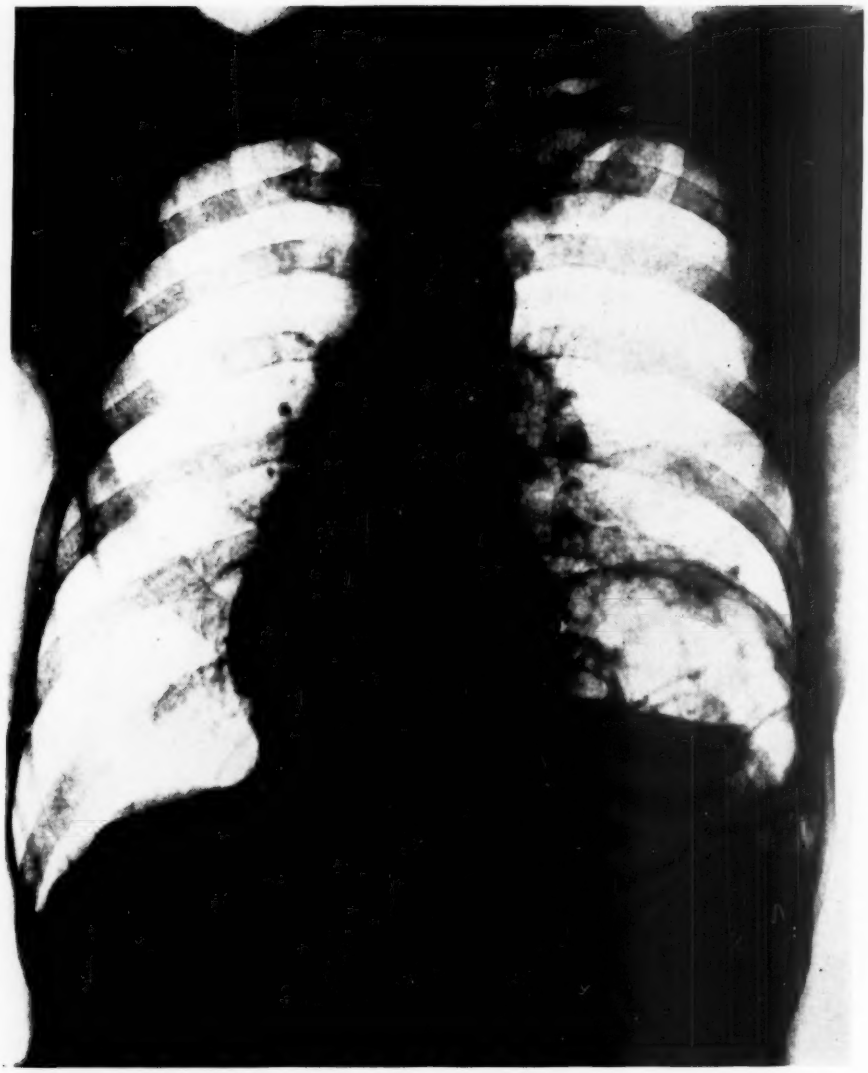

Fig. 2.—Teleroentgenogram made the day after the termination of a paroxysm of diaphragmatic flutter.

Exclusive of electrocardiographic and fluoroscopic findings, certain features of the clinical picture presented here have offered bedside evidence arguing against a diagnosis of acute coronary accident, should this same individual be encountered by the reader. Foremost was the absence of pain across the upper chest, and the alleged radiation of pain from the region of the cardiac apex into the left arm. Of almost equal significance was the behavior during the attack, the patient moving about more actively with his histrionics than does the usual victim relatively immobilized by angina. Finally, it is unlikely that an examiner palpating the throb, or hearing the loud bruit of

the rapidly contracting diaphragm, would associate the complaints with the heart for long in the presence of a normal pulse rate. This man will no doubt make more appearances in various hospitals throughout the country, and it is hoped that these observations, along with those previously published, may enable others more readily to arrive at a correct diagnosis. The possibility of diaphragmatic flutter may be called to mind in unusual types of paroxysmal precordial pain.

SUMMARY

Further observations are submitted concerning an individual who presents the syndrome of associated diaphragmatic flutter and pain suggestive of acute coronary insufficiency. Practical differential diagnostic suggestions are made for bedside diagnosis.

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DOUBLE RUPTURE OF THE HEART FOLLOWING MYOCARDIAL INFARCTION

Report of a Case

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AN UNCOMMON complication of myocardial infarction is rupture of the interventricular septum. A subsequent rupture of the ventricular wall is evidently unusual, for a fairly wide search of the literature reveals no report of such a case.

CASE REPORT

A 60-year-old Merchant Marine carpenter entered the hospital on Jan. 21, 1946, complaining of shortness of breath of one week's duration. He had felt perfectly well until one week before admission to the hospital when, early in the afternoon, he noted a "burning" sensation in the epigastrium. His duties were light, and he had not overexerted himself at any time. He rested in the afternoon, and the sensation of burning passed away. On the following day he experienced mild orthopnea and dyspnea, both of which were ingravescent until admission. Four days later there was a recurrence of the epigastric burning, associated with radiation of mild pain from the epigastrium to the right side of the neck and down the right arm, which lasted several hours. Because of the increasing difficulty in breathing, he reported to the hospital.

He gave no past history of hypertension, but his blood pressure had not been taken for several years.

On physical examination, he was found sitting on the side of the bed, moderately cyanotic, extremely dyspneic, and perspiring freely. The rectal temperature was 98.0° Fahrenheit. The pulse rate was 100, and the respirations were 20 per minute. The blood pressure was 105/90. The heart was believed to be enlarged to the left, but the exact degree of enlargement could not be estimated accurately because the chest wall was thick. There was no thrill. There was a presystolic gallop rhythm, heard best over the aortic area. The heart sounds were normal. There was an extremely loud systolic murmur heard at the apex and transmitted over the precordium and the left upper quadrant of the abdomen. Examination of the lungs revealed the presence of medium moist râles over the lower two-thirds of the lungs. The liver was not palpable. There was no ascites. There was minimal ankle edema.

The white blood count showed 16,250 leucocytes, with a differential count of 86 per cent segmented cells and 14 per cent lymphocytes. Urinalysis was negative. The sedimentation was 3 mm. in one hour. A portable chest plate was reported as showing enlargement of the heart to the left with mottling in the lower lung fields, compatible with pulmonary edema. An electrocardiogram showed a Q_3T_3 type of ventricular complex, characteristic of posterior myocardial infarction.

He was placed on complete bed rest and given oxygen continuously by mask. On the second and third days of hospitalization, he had a temperature of 102.0° F. rectally in the late afternoon.

From the Johns Hopkins Hospital, Baltimore.
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Because of the signs of severe cardiac failure, he was given digitalis orally. He received 0.3 Gm. three times a day on the first day and on the second day, 0.2 Gm. three times a day. Thereafter he received 0.1 Gm. daily. The gallop rhythm disappeared on the second day, and his dyspnea and orthopnea decreased. For the first two days his fluids were limited to 1,000 c.c. of liquid, and he was given a low-salt diet. Morphine was occasionally used at night for the relief of his orthopnea. The medium moist râles, heard at the time of admission, receded but never completely disappeared.

On the second hospital day, several petechiae were noted on the dorsal surface of the right foot. A tourniquet test, bleeding, and clotting times were normal. Blood cultures were sterile. He appeared to be improving rapidly on the second and third days. Each day a few more petechiae appeared until at death on the seventh day, they were widely distributed over the body. None ever appeared on the mucous membranes or in the retinae. The blood pressure remained at 105/90, and the systolic murmur at the apex remained unchanged. The pulse was always regular.

On the fifth hospital day, the orthopnea and dyspnea again became uncomfortable. The patient experienced mild epigastric burning intermittently. The following day ankle edema became moderately severe, and at night he was disoriented. The presystolic gallop rhythm returned on the seventh hospital day. He began to yawn and became incontinent of urine. The ankle edema became severe, and medium moist râles could be heard over all parts of both lungs. He sank into coma and died on the seventh hospital day. Examination of the heart just before death revealed no abnormalities not present at admission. Neurological examination remained normal throughout.

Pathologic Findings.—At autopsy, petechiae were noted over the arms, trunk, and legs. There was pitting edema of the feet and ankles. The pleural cavities contained no fluid. The right lung weighed 700 grams, and the left lung weighed 600 grams. Both lungs were wet and congested on their cut surfaces.

The pericardial sac contained 500 c.c. of dark red blood and clots. The heart weighed 500 grams. There was an extensive infarction of the posterior surface of the heart that involved one-third of the posterior part of the right ventricle, the interventricular septum, and one-third of the posterior inferior part of the left ventricle. Through the lower posterior surface of the left ventricle, there was a ragged, irregularly-shaped rupture of the ventricular wall (Fig. 1). It measured 4 cm. by 1.5 centimeters. There was a second rupture measuring 3 cm. by 1.5 cm. at the base of the interventricular septum, making a passage between the left and right ventricles (Fig. 2). There was complete occlusion of the posterior branch of the right coronary artery, approximately 8 cm. from its orifice. The left coronary artery was patent, but there were many atheromatous plaques present. There were hemorrhages along the distribution of the posterior branch of the right coronary artery, as well as around the infarcted area. The wall of the left ventricle was 2 cm. in thickness, while that of the right ventricle was 0.5 cm. in thickness. There was one mural thrombus adherent to the wall of the right auricle and another adherent in the region of the infarction at the base of the right ventricle. There was calcification of the leaflets of the aortic valve, which prevented complete closure of the valve. Atheromatous plaques were noted in the free border of the mitral valve, as well as in the aorta.

The liver weighed 2,000 grams. The kidneys were grossly normal.

Microscopic examination of the sections of the heart showed an old thrombus with recanalization in the lumen of the posterior descending branch of the right coronary artery. A more recent thrombus superimposed on the old one was demonstrated in sections taken closer to the coronary orifice. There was extensive hemorrhage, muscle necrosis, and polymorphonuclear leucocyte infiltration in the walls of the right and left ventricles and the interventricular septum in the area of the infarction. A thrombus consisting of platelets, fibrin, polymorphonuclear leucocytes, and red blood cells was adherent to the endocardium of the right auricle.

In one section of the lungs, a small infarct of the pleura was seen and, in another section, an embolus consisting of fibrin, red blood corpuscles, and polymorphonuclear leucocytes was present in one of the small pulmonary vessels.

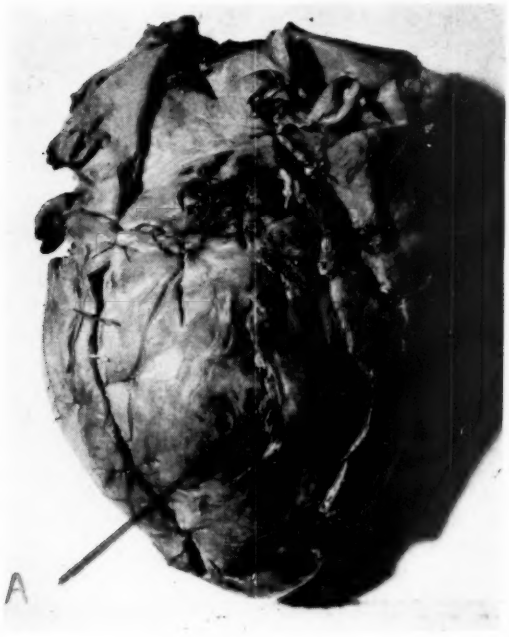

Fig. 1.—The posterior surface of the left ventricle showing the irregular longitudinal rupture (*A*).

Fig. 2.—The interventricular septum as seen from the right side of the heart, and showing a probe through the ovoid rupture of the interventricular septum.

The liver sinusoids were distended with red blood corpuscles in areas adjacent to the central veins, with necrosis of the liver cells bordering the central veins where the distention of the sinusoids was more marked. There was fat infiltration throughout the sections of the liver.

The walls of the arteries of the kidney showed thickening, and an occasional arteriolar lumen was obliterated.

Sections through the petechiae showed emboli consisting chiefly of fibrin located in the capillaries of the corium. There were hemorrhages adjacent to the capillaries.

DISCUSSION

Rupture of the anterior or posterior wall of the left ventricle is far more common than rupture of the interventricular septum. In 1925, Krumbhaar and Crowell[1] summarized all the cases of ventricular wall rupture from any cause and added twenty-two new cases. They were able to find 632 cases in the literature of the preceding fifty years. They tabulated the sex, age, duration of life following rupture, and the apparent exciting cause. They were unable to offer any explanation as to why some infarcted hearts ruptured and others did not.

In 1942, Edmonson and Hoxie[2] reported seventy-two cases of heart rupture of all types, of which thirteen were interventricular septal ruptures. They were able to make the diagnosis in three of their cases ante mortem. They emphasized the importance of keeping patients quiet after a coronary occlusion, especially for the first sixteen days, during which time ruptures were most likely to occur. They also pointed out that ruptures occurred three times as frequently in patients who had a hypertension of more than 140/90 following occlusion than in those who had normal blood pressure.

In 1943, Weber[3] reported a case of interventricular septal rupture. He reviewed the literature up to that time and was able to find thirty-four cases. (Edmonson and Hoxie's cases were not included.) Few of these patients survived longer than a month. None suffered a second rupture. Only five were diagnosed before death. He was, however, able to diagnose his own case ante mortem. He pointed out that the diagnosis of interventricular rupture can be made when a loud systolic murmur and thrill develop suddenly after a known coronary thrombosis. A ruptured chorda tendineae or a ruptured papillary muscle, however, may give the same signs following a coronary occlusion.

In 1945, Segall[4] discussed cardiac rupture and presented four cases. None of these were interventricular ruptures. He mentioned the difficulty in making the diagnosis ante mortem, but noted that sudden death preceded by sudden cardiac pain with severe dyspnea and shock occurring within the first two weeks of the onset of a coronary occlusion, is very suggestive evidence for a rupture of the ventricle with cardiac tamponade.

Levine[5] warns against the use of stimulants in coronary thrombosis: "It is mainly with regard to the dislodgment of an embolus from the ventricular thrombus and rupture of the ventricle that stimulation is to be avoided." Both of these complications occurred in our case following the use of digitalis. For several days the digitalis produced improvement in the pulmonary congestion, as well as in the ankle edema. Whether the digitalis was ultimately harmful is a question which cannot be answered.

The petechiae were an unusual manifestation of embolism from mural thrombi. At autopsy they were found to have originated in the right auricle and ventricle, producing paradoxical embolism.[6]

SUMMARY

A case of coronary occlusion followed by rupture of the interventricular septum and later by rupture of the posterior wall of the left ventricle is presented. Paradoxical embolism was associated.

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ELECTROCARDIOGRAPHIC STUDIES OF GUNSHOT AND STAB WOUNDS OF THE HEART

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TRAUMATIC injuries to the heart present a rare opportunity to observe clinically what has been accomplished experimentally in animals. The close observation of all such cases may do much to knit more closely the results of clinical cardiovascular examinations with the known pathologic physiology of the heart.

For more than forty years stab and gunshot wounds of the heart have been treated surgically. Davenport,[1] in 1924, reported the appearance of the typical electrocardiographic curves following ligation of a branch of the descending coronary artery and vein, after which similar reports were published by Elkins and Phillips,[2] Porter and Bigger,[3] Koucky and Miles,[4] and Davenport and associates.[5]

That an inflammatory reaction of the pericardium is a universal complication of penetrating injuries of the heart has been recognized for many years. Hesse,[6] on the basis of a review of the aftereffects in twelve cases of his own and 107 cases from the literature, stated that the appearance of a dry pericarditis after heart suture could almost be considered a rule. Beck[7] mentioned the high incidence of postoperative pericardial effusion and subsequent pericardial adhesions. In dogs, Barnes and Mann[8] have shown that the mere opening of the pericardium resulted in extensive pericarditis.

The electrocardiographic changes produced by pericarditis consisted of early and transient elevation of the R-T segment in the first two, or in all three, leads.[9] This elevation is generally most marked in Lead II, and aptly, therefore, has been called the T_2 type by Wood.[10] The deviation is in the same direction (upward) in all (three) leads, unlike myocardial infarction where it is opposite in direction in Leads I and III. Also no significant Q pattern develops.

The electrocardiographic picture of acute myocardial injury, on the other hand, depends upon the location of the injury. Thus, an injury of the anterior left ventricular walls produces the characteristic T_1 type, with early upward elevation of the RS-T segment in Lead I. Infarction of the posterior or basal part of the left ventricle produces changes in the RS-T segment and T wave which are practically the reverse of those occurring in anterior infarction; the

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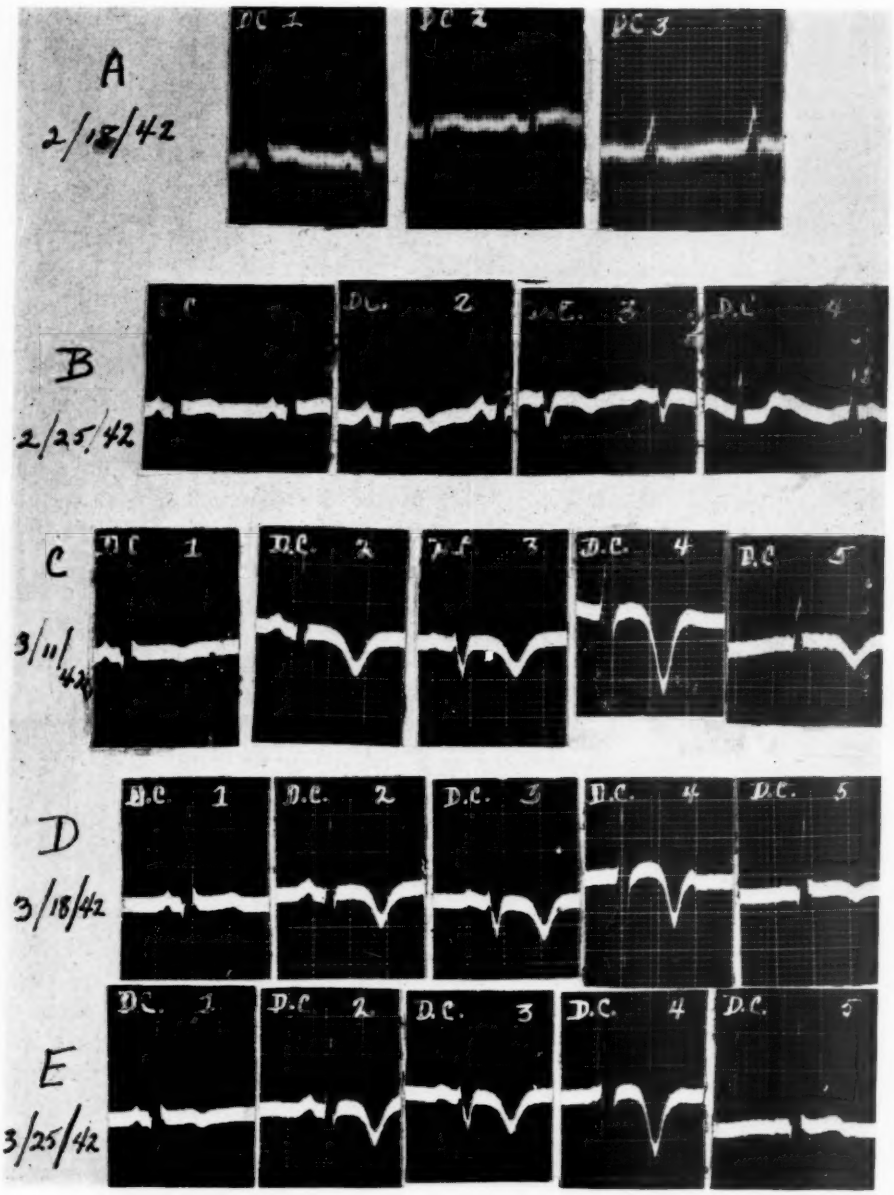

Fig. 1.—Case 1. D. C., a 26-year-old Negro man. Bullet wound, anterior axillary line. *A*, Obtained three days after accident; *B*, obtained one week later; *C*, obtained three weeks later; *D*, obtained four weeks later; *E*, obtained five weeks later; *F*, obtained six weeks later; *G*, obtained three months later; *H*, obtained nine months later; *I*, obtained fourteen months later; *J*, obtained thirty-seven months later.

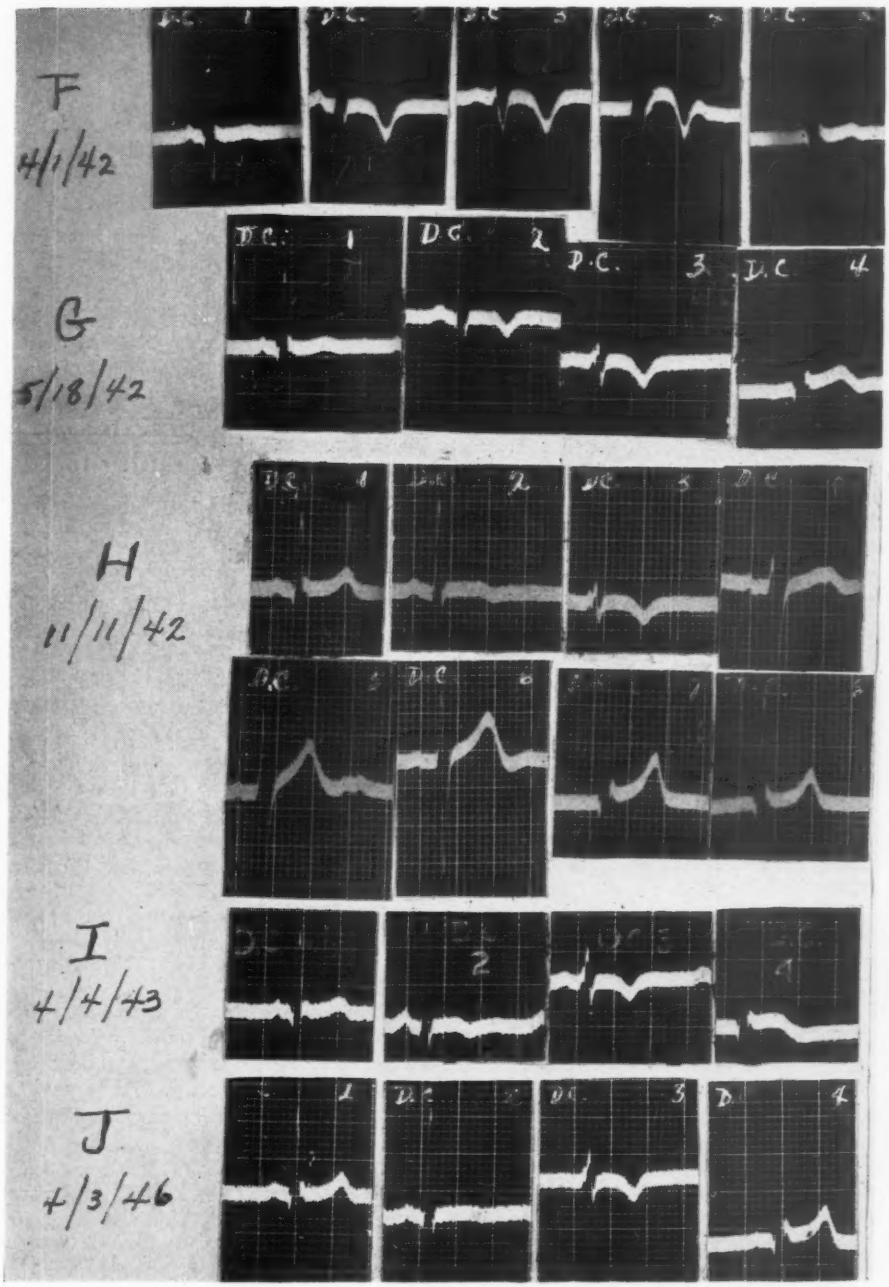

Fig. 1.—Cont'd. For legend see opposite page.

T_3 type (and usually the T_2 type) being inverted, and the T_1 type remaining upright. The RS-T shift is upward in Lead III and downward in Lead I.

Two case reports are presented from the records of the Indianapolis City Hospital. In the first patient, a pistol bullet pierced the anterior portion of the apex of the left ventricle and lodged in the pericardial sac; in the second patient the right auricle was injured by an ice pick.

CASE REPORTS

CASE 1.—D. C., a 26-year-old Negro man, was admitted to the Indianapolis City Hospital on Feb. 14, 1942, at about 11:00 P.M., after receiving a bullet wound in the anterior axillary line at about the fifth intercostal space.

On admission, he was in profound shock. His pulse rate was about 110 beats per minute and the heart sounds were distant. Fluoroscopy of the chest revealed a globular pericardial shadow with only slight movement.

A surgical operation* was started about an hour after admission. Upon entering the pericardium a large amount of fluid was encountered. At the tip of the left ventricle, three wounds were discovered, each approximately 1.0 to 2.0 cm. in length. Two of these were on the posterior surface of the apical region of the left ventricle, and one on the anterior surface. The posterior wounds were bleeding profusely. All of the wounds, and the pericardium as well, were closed with interrupted silk sutures. After operation, the blood pressure, which had been considerably lower, rose to 125/85.

Roentgenograms of the chest obtained two days, then one, two, and three weeks after the operation, revealed the cardiac shadow displaced to the right and pleural effusion of the left side.

Twelve electrocardiograms were obtained between the third day and thirty-seven months after the operation. Ten of them are shown in Fig. 1. In *A*, obtained three days after the accident, the RS-T segment was slightly elevated in Leads I and II and isoelectric in Lead III with a negative T wave. There was an S wave in Lead III. In *B*, obtained one week later, the RS-T segment was elevated in Lead I and depressed in Lead IV F. The T wave was inverted in Leads II and III. In *C*, obtained three weeks later, there was a cove-plane T wave in the limb leads and in Leads CF_2 and CF_4. In *D*, obtained four weeks later, there was a positive T wave in Lead I. In *E*, obtained five weeks later, there was a negative T_1 and a positive T_4. In *F*, obtained six weeks later, T_1 was positive and the T wave was less negative in Lead CF_2. In *G*, obtained three months later, there was an elevated RS-T segment in Lead IV. In *H*, obtained nine months later, there were less negative T waves in Leads II and III and taller T waves in Leads I and IV F. In *I*, obtained fourteen months later, there was a less positive T_1 and T_4. In *J*, obtained thirty-seven months after the operation, there were taller T waves in Leads I and IV F and diphasic T waves in Lead II.

CASE 2.—J. C., a 40-year-old Negro man, was admitted to the Indianapolis City Hospital on Aug. 14, 1943, about one-half hour after receiving a stab wound of the chest. On admission, he was in profound shock. The arterial blood pressure could not be recorded and the pulse was imperceptible at the wrist. The heart sounds were not audible. Fluoroscopy of the chest showed a quiet, dilated, globular heart. Forty minutes after admission, a surgical operation† was started. The pericardium was opened and a large quantity of blood freed. It was found that a cut approximately one-quarter of an inch in length penetrated the right auricle. Three sutures were used to close the wound. In ten minutes, the arterial blood pressure was 120/70. In two weeks, the patient was up in a wheel chair, and about ten days later, the patient was released after an uneventful recovery.

Roentgenograms of the chest were obtained one and two months after the operation and revealed clear lung fields, a transverse cardiac diameter of sixteen centimeters, and a "bottle-

*Performed by Dr. Wayne Carson, Indianapolis.

†Performed by J. R. Eastman, Jr., M.D., Resident in Surgery, Indianapolis City Hospital.

shaped" cardiac shadow. At the end of the second month, the transverse cardiac diameter measured fifteen centimeters.

Several electrocardiograms were taken over a period of two months after the operation, four of which are shown in Fig. 2. *A*, obtained three days after the operation, revealed that the RS-T segment was elevated 2.0 mm. above the isoelectric line in Leads I, II, and IV F, and isoelectric in Lead III with an inverted T wave and an S wave. The pulse rate was 100 per minute. In *B*, obtained one week later, the T waves were taller in Leads I, II, and IV F, and absent in Lead III. In *C*, obtained two weeks later, the T waves were inverted in Leads I, II, and IV F. The pulse rate was 100 per minute. In *D*, obtained eight weeks later, the T waves were positive in Leads I and II, diphasic in Lead III, and less negative in Lead IV F. In Lead III, the S wave was less than 2.0 millimeters. The P-R interval measured 0.24 second. The arterial blood pressure was 160/90. The pulse rate was 80 per minute. The transient changes in the electrocardiogram indicated acute pericarditis.

DISCUSSION

In the two patients there was no history of heart disease previous to the accidents, nor of any other illness which might have predisposed to such disease.

In Case 1, the electrocardiograms made from the third day to the thirty-seventh month after the heart wound showed progressive changes in the R-T segments and cove-plane T waves. In three months the T waves were positive in Leads I and IV F, and in the last electrocardiogram, the T waves were positive in Leads I, II, CF_2, and IV F, and negative in Lead III.

The unusual finding in these tracings was the fact that the cove-plane T waves were present in all leads. The electrocardiographic picture of acute myocardial injury of the anterior left ventricular walls usually produces the characteristic T_1 type, with the early upward deviation of the RS-T segment in Leads I and II and a downward displacement of this segment in Lead III, followed by the inversion of T_1 and T_2, with T_3 remaining upright. White[11] states that when T waves are inverted in all three classical leads, we are dealing either with multiple areas of infarction, coronary insufficiency, extensive pericarditis complicating infarction or occurring without myocardial infarction, or rarely, with myxedema. Thus, the three areas of infarction in this case were indicated by the cove-plane T waves in the three classical leads, and also in Leads CF_2 and CF_4. The prolonged duration of the changes of the RS-T segment suggest myocardial damage.

In Case 2, the electrocardiograms which were made from the third day until eight weeks after the injury showed changes in the RS-T segments and inverted T waves. On the third day, the RS-T segments were elevated 2.0 mm. above the isoelectric level in Leads I, II, and IV F; and for the next two weeks the T waves were inverted in the same leads and in Lead III, but less negative in Lead IV F. The P-R interval measured 0.24 second. The transient changes in the electrocardiogram suggested acute pericarditis.

Injury to the auricle alone is rare. On review of the literature, I found four cases with electrocardiographic tracings. The first case, reported by Glasser and associates,[12] was a gunshot wound of the left auricle in which they describe the changes of the electrocardiogram as resembling the changes of an anterior infarction. The second case, reported by Caviness and Turner,[13] was a stab wound of the left auricle. They describe the changes in the electrocardiogram

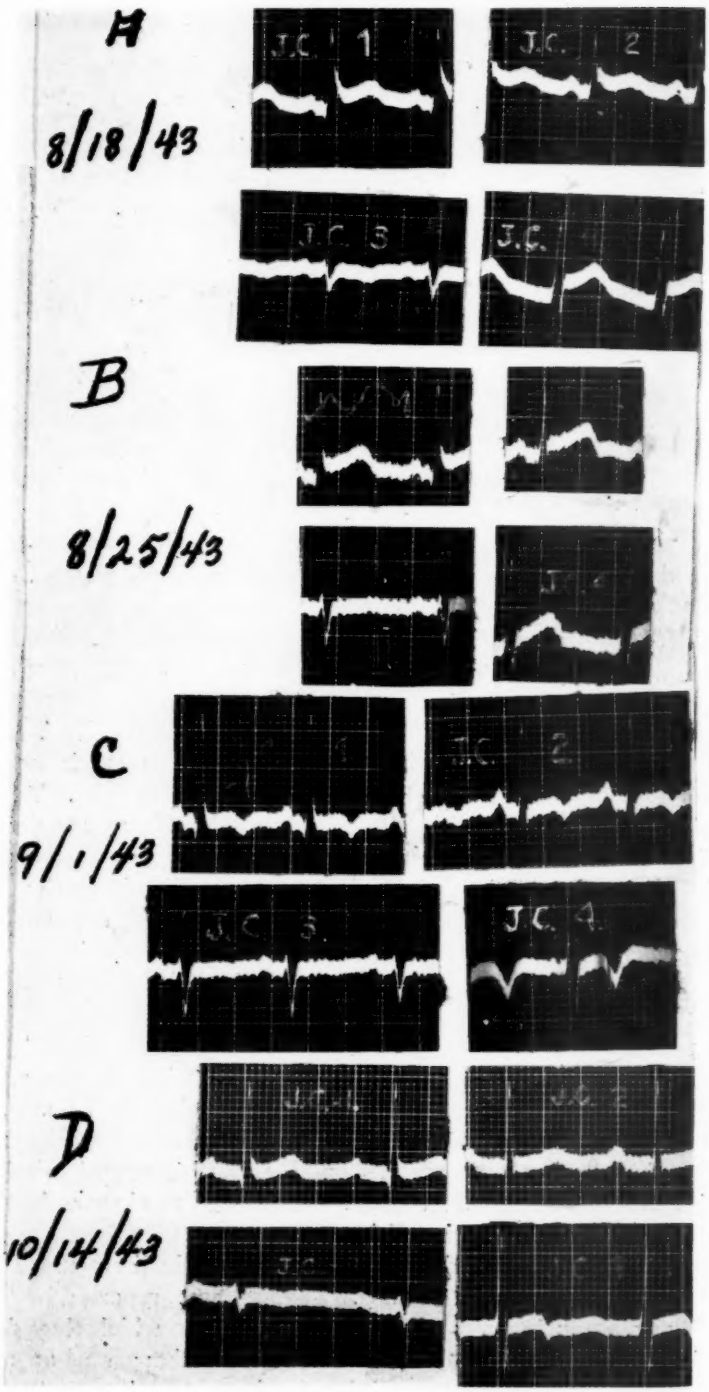

Fig. 2.—Case 2. J. C., a 40-year-old Negro man. Stab wound of the chest. *A*, Obtained three days after operation; *B*, obtained one week later; *C*, obtained two weeks later; *D*, obtained eight weeks later.

as those produced by coronary occlusion. There were inverted T waves in all leads. The third case, reported by Thompson,[14] was a stab wound of the left auricle. There was inversion of the T waves in all four leads. He describes the changes as those of acute pericarditis. The fourth case, reported by Vander Veer and Norris,[15] was a stab wound of the right auricle. An electrocardiogram made fifteen hours after operation revealed elevated RS-T segments in Leads I and II and some slurring of the descending limb of the R wave. They state that the changes in the electrocardiogram were due to acute pericarditis, and not to the injury of the auricle alone.

SUMMARY

The electrocardiographic studies of two patients with cardiac trauma, one with a gunshot wound of the apex of the left ventricle, and the other with a stab wound of the right auricle, are reported.

In Case 1, the electrocardiographic picture of acute anterior coronary infarction is in keeping with the preoperative diagnosis of three wounds, one on the anterior surface and two on the posterior surface of the apex of the left ventricle.

In Case 2, with a stab wound of the right auricle, the electrocardiographic changes reveal prolongation of P-R intervals to 0.24 second. The other changes in the electrocardiographic pattern may be attributed to acute pericarditis.

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THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN IN BEESWAX-PEANUT OIL: GLUTEAL ABSCESSES AND RUPTURE OF THE SPLEEN

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THE work of Romansky and Rittman[1-3] suggests that the intramuscular injection of penicillin in a beeswax-peanut oil mixture would be a convenient and effective method of administration in almost any condition in which the drug is indicated. However, a review of the literature reveals that there are several disadvantages in using this procedure in patients with subacute bacterial endocarditis. The case reported here presents an added objection.

The first point against the use of penicillin in beeswax-oil is that the large doses given by this method are less effective in producing an adequate penicillin blood level than is the prolonged intermittent administration of the same amount of penicillin in an aqueous medium. This has been pointed out by Kirby and associates.[4] Apparently, when in contact with body fluids at body temperature, the penicillin in beeswax-oil is partially destroyed so that only one-half to one-third of the penicillin, as measured by present methods, reaches the blood.

A second point against penicillin in beeswax-oil is that the blood levels obtained with it are unpredictable. Kirby and associates[4] found that 12 per cent of their patients had a blood level of less than 0.07 unit per c.c. four hours after the injection of 300,000 units of calcium penicillin in one c.c. of beeswax-peanut oil. Four hours was the time at which the average penicillin blood level was the highest, that is, 0.44 unit per cubic centimeter. Thirty per cent of their patients had no penicillin in their blood after twelve hours. Romansky and Rittman,[3] using a slightly different method of measurement, obtained values just twice those of Kirby and associates. The peak blood level was at four hours, but the average value was 0.99 unit per cubic centimeter. Fourteen per cent had a level of 0.16 unit per c.c., or less, at four hours, and 30 per cent had no detectable penicillin in their blood after twenty-four hours. In contrast to the foregoing, continuous intravenous drip produces a blood level of about 0.1 unit for every 100,000 units administered in twenty-four hours, and the variations from this level depend primarily on controlling the rate of flow.[5,6] A similar relationship holds for continuous intramuscular drip.[7] The current trend in the treatment of subacute bacterial endocarditis is to give between 200,000 and 500,000, or

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more, units per day for three to eight weeks and to maintain at all times a blood level which is four to five times that of the sensitivity of the organism.[8-11] With penicillin in beeswax-oil, such a program requires frequent blood levels to determine the effectiveness of the therapy, and the beeswax-oil must be administered two to three times a day.

A third point against the use of this oil is that beeswax and peanut oil are foreign substances which can cause considerable tissue reaction. Romansky and Rittman[2] reported that after injection of a mixture of the two substances into the muscles of the hamster there was an infiltration of polymorphonuclear leucocytes about the injection site at the end of twenty-four hours with no evidence of muscle necrosis. By the tenth day after injection there were foreign body giant cells, mononuclear leucocytes, and oil cysts 1.0 to 2.0 mm. in diameter. By the twentieth day, there were minute cysts with fibrous walls, giant cells, and leucocytes. On the thirtieth day the cysts were partially collapsed and the giant cells still persisted.

A corollary of this third point is that these foreign substances are capable in some individuals of causing muscle necrosis and they may be conducive to abscess formation. Especially is this true in the treatment of subacute bacterial endocarditis where large amounts of the agent must be injected repeatedly for a long period. Denton[12] observed marked fibrosis of muscle in a patient suffering from subacute bacterial endocarditis. Denton's patient was given 300,000 units of penicillin in 1.0 c.c. of beeswax-oil twice a day for two months. The sites of injection were varied as widely as possible; but, nevertheless, at the end of this time the muscles became quite indurated, and contained firm nodules about 2.0 cm. in diameter. In spite of this he still had full use of his muscles. In view of the experiences to be quoted here it was believed that some of the nodules might have been the result of abscesses occurring at the sites of the penicillin in beeswax-oil injections; particularly since Denton's patient was not cured until penicillin was given by a different method.

REPORT OF A CASE*

A 17-year-old high school girl was admitted to the Massachusetts General Hospital because of low-grade fever, weakness, pallor, and swelling of the ankles.

At the age of 3 years, following acute appendicitis and appendectomy, she developed migratory polyarthritis, a heart murmur, and chorea. This was diagnosed as rheumatic fever and she was kept in bed for six months. After that she was placed on slightly restricted activity and remained well until the age of 7 years. She then had a second episode of migratory polyarthritis of unknown duration. Following this she was well until six months prior to admission, when she developed pain in the right leg radiating from the knee downward. This followed twisting her leg while swimming. The pain was relieved by manipulation by a chiropractor. Two weeks later she caught a "head cold" with fever of 99° to 100° F., and noted pain in the left upper abdominal quadrant on deep inspiration which lasted two days. Five months before admission she was admitted to another hospital because of a temperature of 101° Fahrenheit. She was given sulfadiazine for seven days during which time she developed a generalized skin eruption. The sulfadiazine was stopped and penicillin was given for three days. The fever disappeared and she

*This case was previously reported at the Massachusetts General Hospital Pathological Conference.[24]

went home where she remained well until four months before admission, when she was again hospitalized for ten days because of a low grade fever and coryza. She was again treated with sulfadiazine and penicillin and remained well for two months. Two months before admission she began to have mild fever, muscle aches, cough, and minimal ankle swelling. She spent three weeks in bed, but when again ambulatory she continued to have ankle swelling that was relieved by rest. During the two weeks before admission her daily temperature varied from 98.6° to 101° Fahrenheit. The night before admission she was nauseated, vomited, and complained of abdominal pain. She had lost about 30 pounds during the six months' illness.

On physical examination she was found to be a pale, well-developed girl in no distress. The temperature was 99.6° F.; the pulse, 95 per minute; and the blood pressure, 130/80. On the cushion and tip of the left thumb there were two red, nontender, punctate areas. She had three carious teeth. The left border of the heart was 12 cm. to the left of the midline in the fifth intercostal space. There was a systolic apical thrill. A forceful mitral first sound was followed by a blowing Grade 4 systolic murmur. No diastolic murmur was heard. The pulmonic second sound was louder than the aortic second sound. The lungs were clear. The nontender tip of the spleen was felt. There was an appendectomy scar. No ankle edema was present.

On admission the erythrocyte count was 3.5 million; hemoglobin, 8.2 Gm.; leucocyte count, 21,700, with 82 per cent polymorphonuclear cells, 10 per cent lymphocytes, 7 per cent monocytes, and 1 per cent eosinophils. The urine was acid and the specific gravity, 1.020. One-plus albumin was found, and two red cells and twenty-five white cells were present in the sediment. The sedimentation rate was 1.45 mm. per minute (normal less than 0.35 mm. per minute). An electrocardiogram was normal with a rate of 100 per minute and normal P-R interval. A chest x-ray revealed a large left auricle posteriorly and elevation of the left main bronchus, consistent with mitral valvular disease.

On the second hospital day the petechiae on her thumb had disappeared and a red "spot" was found on the flexor surface of the right wrist. She vomited several times this day, but had no new complaints. The fifth day she felt well, though her temperature was 104.5° Fahrenheit. She had a slight nonproductive cough. There was definite dullness with bronchial breathing, increased whispered voice, and decreased tactile fremitus over the left lower lobe. A chest x-ray the following day verified the diagnosis of left pleural effusion with displacement of the heart to the left, suggesting the possibility of collapse of all or a portion of the left lower lobe. On the tenth day a shower of small petechiae appeared on the forearms and hands bilaterally and one small petechia in the right lower conjunctival sac. By the eleventh day ten blood cultures had been taken. Of these, two were sterile, one was negative for Brucella organisms, and seven were positive for alpha hemolytic streptococcus of the Lancefield Group A. By this time she was having daily temperature spikes of 103° to 104° F. rectally. Her pulse rate varied from 100 to 110 per minute. On the eleventh hospital day specific treatment was begun. This consisted of 300,000 units of penicillin in 1.0 c.c. of beeswax-peanut oil every eight hours intramuscularly. Fluids were limited to 1,800 c.c. daily. By the fifteenth hospital day, four days after the onset of therapy, her temperature was normal. She did very well until the twenty-fourth day when she had a slight temperature rise to 100.0° F. rectally. She complained of nausea, anorexia, and a periumbilical discomfort for one day only. For the next few days she also complained of a dull ache in the muscles of the right anterior thigh. At the time this was thought to be due to the penicillin injections. A throat culture grew out a few beta hemolytic streptococci. The penicillin sensitivity of the blood organisms was determined. The organism grew in 0.03 unit of penicilin and was inhibited by 0.06 unit. On the twenty-fourth hospital day the penicillin level in the blood at the end of eight hours (just prior to the next injection) was at least 0.06 unit per c.c. and less than 0.24 unit per cubic centimeter. A blood culture that day grew *Staphylococcus albus* (probably a contaminant). On the thirty-second day the penicillin level was less than 0.06 unit per c.c. at the end of eight hours. Benzoic acid, 2.0 Gm. administered three times a day by mouth, was then started.

On the thirty-sixth hospital day the patient complained of an aching pain in the mid-epigastrium and left epigastrium. There was no cough and the pain was questionably aggravated by respirations. The abdomen was soft but there was mild tenderness in the left upper quadrant. Peristalsis was slightly hyperactive. The dullness over the left lower lobe was unchanged from

the previous findings. She had no râles. The temperature was normal and the pulse rate varied from 90 to 100 per minute. This aching pain persisted slightly the next day. The leucocyte count was 20,000, with 73 per cent neutrophils, 13 per cent lymphocytes, and 14 per cent monocytes. In the evening of the thirty-seventh hospital day the patient suddenly clutched her left upper abdomen, vomited, and began writhing and groaning. She was pale, cold, and sweating. The heart sounds were rapid and regular. The chest remained unchanged. The abdomen was quite silent and only occasional tinkles were heard. There was no shifting dullness, spasm, or tenderness. She moved her arms and legs freely and all reflexes were equal. She opened her eyes in response to questioning. Oxygen was given and her color improved. She died twenty minutes after the onset of this episode.

Pathologic Report.—On opening the peritoneal cavity there were 600 c.c. of fresh blood and about an equal amount of clotted blood. The clotted blood obscured the spleen and extended down the left side of the abdomen into the pelvis. About the spleen were numerous dense, fibrous adhesions between the stomach, diaphragm, and parietal peritoneum. The surface of the spleen was ragged due to the adhesions, and just anterior to the hilum there was a deep red slit 2.5 cm. in length, which appeared to be the point of rupture into the peritoneal cavity. In the upper pole there was an abscess cavity measuring 4 x 2 cm. that contained yellow, purulent exudate. Cultures of this abscess revealed alpha hemolytic streptococci. In the lower pole there was a similar cavity measuring 6 x 3 cm. that was partially filled in with scar tissue and contained a small amount of purulent material in the center. In the center of the spleen there was an area 8 x 10 cm. in diameter composed of clotted blood. The splenic artery and vein were normal. There was no normal-appearing splenic tissue. The spleen weighed 630 grams. Microscopically, the cords of the spleen showed a fibrous thickening and many polymorphonuclear cells were present. Surrounding the areas of infarction there was increased fibrous tissue formation and an inflammatory cell reaction with polymorphonuclear cells and frequent phagocytes. There were numerous red cells.

On cut section of the kidney there was good delineation in all the kidney architecture, but the parenchyma appeared paler than usual. There were all degrees of glomerular hyalinization. Parts of the glomerular tufts were hyalinized, and in some glomerular spaces there was hemorrhage. The picture was consistent with healing embolic nephritis without fresh lesions. The right pleural cavity was normal.

The left pleural cavity contained dense fibrous adhesions between the parietal and visceral pleura over the left lower lobe, and between the left lobe and the diaphragm. The cavity contained 200 c.c. of clear, straw-colored fluid. Cut sections of the lungs revealed the parenchyma to be mottled pinkish-red and there were several small areas of atelectasis in the left lower lobe.

There was a small amount of fibrous adhesion between the visceral and parietal pericardium at the apex of the heart. The heart weighed 360 grams. The myocardium was paler than usual. The chordae tendineae of the aortic leaf of the mitral valve were somewhat shortened and thickened, and at the free edge of this valve there was a 2 x 3 mm. hard vegetation, the surface of which was rough and friable. The valve was also thickened. The remaining valves were normal. Microscopically, on the surface of the mitral valve there was a platelet thrombus incorporating bacterial masses with scarring and granulation tissue around them. Several giant cells were present. The thrombus was attached to the collagenous valve leaflet whose periphery was rather cellular. The process, therefore, appeared almost healed.

When an incision was made across each buttock to examine the injection sites of the penicillin in beeswax-oil, a large amount of purulent, yellow exudate oozed from the deep tissues. This exudate arose from numerous small abscesses in the substance of the gluteus maximus muscle and a few abscesses in the deeper layers of fat in the gluteal region. A culture of this revealed alpha hemolytic streptococcus, presumably the same organism that had been in the patient's blood stream originally. In several of these abscesses a darker-colored, thick oily fluid was also present, which had the appearance of the oil-beeswax vehicle that had apparently been injected directly into the previously formed abscesses. Microscopically, there was muscle necrosis and inflammatory reaction with foreign body giant cells, polymorphonuclears, lymphocytes, and histiocytes. There was also basophilic material present, presumably the wax in which the penicillin was incorporated.

DISCUSSION

Rupture of the spleen has been reported to be common in malaria, typhoid fever, pregnancy, parturition, acute infections, leukemia, typhus fever, infectious mononucleosis, relapsing fever, and many other conditions, but we have been able to find only ten reported cases in subacute bacterial endocarditis.[16-25]

The histologic structure of the spleen facilitates bacterial embolism and infarction. Examination of the spleen in subacute bacterial endocarditis will reveal, in nearly all cases, the presence of small infarcts. The formation of a splenic abscess is the result of a septic embolus with necrosis and breakdown of the area of infarction.

Lake and co-workers,[16] who reported the first case of ruptured spleen in subacute bacterial endocarditis, believed that the infected infarct had ulcerated through the splenic artery. This was also probably true in our case. Six of the ten cases reported in the literature had rupture of an infected infarct or frank abscess.[16,17,20-23] The patient reported by Favour and associates[9] had received intensive penicillin therapy, and at death the splenic infarcts and blood were sterile. Pallasse and associates[19] gave as the cause of hemorrhage the rupture of a cortical infarct; Hertzog and co-workers,[25] the rupture of a hemorrhagic infarct. Krokeiwicz[18] stated that the cause was due to paroxysmal increasing blood pressure when the patient strained during defecation. His patient was the only one of the ten to have proven involvement of the left pleura as a result of the subdiaphragmatic inflammation.

The reason for the choice of therapy in our patient was that the organism grew in 0.03 unit of penicillin per c.c. and was inhibited by 0.06 unit. Kirby and co-workers[4] reported 96 per cent of their patients had a blood level between 0.04 and 1.0 units per c.c. eight hours after the injection of 300,000 units of calcium penicillin in beeswax-oil, and so it was believed that an injection every eight hours should prove sufficient. However, the precaution suggested by Keefer and associates[13] of distributing the injection sites in the hips, arms, and thighs was not observed and injections were given alternately in each buttock. The bacterial endocarditis in our patient did respond to the penicillin therapy given. As was indicated in the pathologic examination, the lesions on the valve leaflets were almost healed.

The development of the alpha hemolytic streptococcus abscesses at the sites of penicillin injections has not been reported before. However, continuous intravenous or intramuscular drip has not infrequently been accompanied by considerable local reaction. Morgan, Christie, and Roxburgh,[14] who first reported the use of continuous intramuscular drip, noted two abscesses due to *Coliform bacilli* around the site of the infection. Smith and Harford[7] found that ten out of sixteen patients treated with continuous intramuscular drip developed severe local inflammatory reactions at the injection site at about the fifth to seventh day. This consisted of local leucocytosis, local pain, redness, heat, and swelling involving the whole lateral aspect of the thigh, all of which subsided in twenty-four hours after changing the injection site. Nelso-Jones and Williams[15] reported a case of subacute bacterial endocarditis in which the

site of the continuous intramuscular drip was changed every four to five days, and twelve days after each site was changed a sterile abscess developed. This patient received 120,000 to 150,000 units of penicillin per day in the form of 1,000 units per c.c. in distilled water at pH 6.5. Fifteen c.c. of dark cream-colored, purulent fluid which was sterile aerobically and anaerobically was obtained from each abscess, which then proceeded to heal uneventfully.

The tissue reaction which occurred about the sites of injection of penicillin in beeswax-peanut oil was probably primarily due to the beeswax-peanut oil. The beeswax-peanut oil being a foreign body produced localized areas of necrosis which were easily invaded by bacteria producing abscesses. These abscesses were presumably infected by the organism of the blood stream despite the presence of penicillin in nearby tissues which apparently did not diffuse into the abcesses. Furthermore, much of the penicillin that was injected directly into abcesses already present was poorly utilized, if at all. Had aqueous penicillin been used perhaps these abscesses would not have occurred.

SUMMARY

1. Penicillin in beeswax-peanut oil led to the development of autogenous abscesses at the injection sites in a patient with subacute bacterial endocarditis. Death in this patient resulted from rupture of a splenic abscess.

2. Penicillin in beeswax-peanut oil is not the method of choice for the long-term treatment of subacute bacterial endocarditis.

3. A review of the literature on ruptured spleens in subacute bacterial endocarditis revealed only ten reported cases.

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Abstracts and Reviews

Selected Abstracts

Meccheri, L. A.: On the Pathological Variations of Venous Pressure. Publ. d. Centro de invest. tisiol. **9**:237, 1945.

The author studied the value of venous pressure determinations in more than 100 cases with various cardiac and mediastinal syndromes. His conclusions are the following:

(1) A general increase of venous pressure is caused by cardiac disturbance, while a regional increase is due to compression of a collector. (2) General venous hypertension indicates heart failure; general venous hypotension, peripheral failure. (3) In diseases of the respiratory system, venous pressure determinations may be useful. Hypertension indicates corpulmonale; hypotension, a peripheral disturbance. (4) Cardiac edema, cyanosis, and hepatic enlargement may be differentiated from other types by a high venous pressure, which is observed when these signs are caused by cardiac failure. (5) Serial determinations may help in the evaluation of cardiac failure and of the results of treatment. (6) Pleuropulmonary and mediastinal syndromes may cause regional changes of venous pressure. These may be evaluated only by measurements in different veins. (7) Increase of venous pressure in one venous collector may be the only sign of initial compression.

It should be noted that general venous hypertension, not connected with cardiac failure, may be found in tricuspid valve defects; in some cases of adhesive pericarditis; in some aneurysms (compression of the right auricle); in Lutembacher's syndrome; and, possibly, in auricular septal defects.

LUISADA.

Espersen, T., and Dahl-Iversen, E.: The Clinical Picture and Treatment of Pheochromocytomas of the Suprarenal. Acta chir. Scandinav. **94**:271 1946.

The authors review the embroyology, reported cases, and clinical picture of pheochromocytoma of the adrenal and add two cases of their own. The first, a man of 49 years with paroxysmal hypertension associated with violent headaches and cardiac irregularity, had a goiter and a basal metabolic rate of plus 30 per cent. The frequency of his attacks was reduced by thyroidectomy and he improved further on methyl-thiouracil, but eventual laparotomy revealed a 1,400 gram tumor. In the second case a boy of 10 years with permanent hypertension was explored through a left lumbar incision and no tumor could be found. Death a few hours after operation followed a shock state, and necropsy disclosed a small tumor in front of the great vessels and connected with the left adrenal by a small pedicle.

The level of epinephrine was found to be elevated in the blood of both patients, especially during attacks, and the tumors contained considerable amounts of it. The thyroid hyperplasia and improvement under antithyroid measures are attributed by the authors to a relation between the thyroid, adrenals, and hyperepinephrinemia analogous to that obtaining in certain cases of Graves' disease. They emphasize the value of methyl-thiouracil and preoperative attention to salt and water balance to minimize the danger of shock postoperatively. They now favor the abdominal approach for all cases.

SAYEN.

Elmquist, A., and Liljestrand, A.: On the Chemical Evaluation of Digitalis With the Baljet Reaction. Acta physiol. Scandinav. **12**:53 (No. I), 1946

The Baljet reaction, a red-orange color formed when active cardiac glycosides are mixed with an alkaline picrate solution, has been modified in various ways since its discovery in 1918. The authors investigated the reliability of an electrophotometric technique devised by Bell and Krantz in 1939, which is claimed to possess accuracy comparable to that of cat biological assay. They report that the color was as strong in old solutions of *Digitalis purpurea* and *Digitalis lanata* as in fresh solutions, whereas the biologic potency, as assayed in guinea pigs, declined significantly. Warming the solutions further decreased biological assay activity, but the Baljet reaction was as intense as at room temperature. Digitonin (active) could be added to solutions without increasing the color reaction. It is concluded that the Baljet reaction is unreliable for clinical purposes.

SAYEN.

Troeme, P. Micronodular and Reticulated Appearance of the Lungs During Acute Broncho Pulmonary Infection in a Patient With Mitral Disease. Arch. d. mal. du coeur **39**:453 (Nov.-Dec.), 1946.

A case is reported in which the lung fields presented the peculiar granular appearance described a year ago by Leblanc as occurring in the course of mitral disease. In the present case, an x-ray film made during an attack of acute bronchitis in a patient who had mitral stenosis showed, in addition to reticulation, small shadows having the appearance of nodules scattered throughout the lung fields. As in Lebanc's case, the picture was strongly suggestive of tuberculosis, from which the condition may be difficult to differentiate. The peculiar lung shadows are evanescent.

LAPLACE.

Servelle, M. Lymphography and Elephantiasis. Arch. d. mal. du coeur **39**:409 (Nov.-Dec.), 1946.

Lymphography is described as a new procedure of great value for physiopathologic study and for the diagnosis of elephantiasis, lymphedema, and related conditions. This report is concerned primarily with elephantiasis which is not an unusual condition in France.

Twelve cases of elephantiasis are reported, in eleven of which the lower extremity was involved. Extensive radiologic studies, including lymphography, were carried out. Commenting on these cases, the author states that he has found no evidence of deep venous thrombosis in any cases of elephantiasis, but that venography is essential to differentiate elephantiasis from postphlebitic edema which it resembles. There is risk of serious complications if the surgical treatment of elephantiasis is applied to postphlebitic edema.

Lymphography is cases of elephantiasis demonstrates dilatation and elongation of the lymphatics predominately on the internal aspect of the calf. The existence of marked lymphostasis is clearly demonstrated by making successive films during drainage of the contrast medium from the leg. It is uncertain whether the stasis is due to dilatation of the lymphatics or vice versa, but it is quite apparent that they coexist.

The pathogenesis of lymphedema is, in the majority of cases, an infection, sometimes due to insect bites involving the inguinal and retrocrural lymph nodes. The author does not believe any specific infection is involved. He emphasizes the necessity for special care in the treatment of inguinal adenitis in order to prevent elephantiasis. The relative effectiveness of the various operations designed to establish lymphatic drainage is discussed. Of these, two stage total superficial lymphangiectomy, although a relatively shocking procedure, has given excellent and, by far, the best results.

LAPLACE.

Lian, C., and Mantoux, G.: Syncope and Bundle Branch Block. Arch. d. mal. du coeur **39**:438 (Nov.-Dec.), 1946.

Fourteen cases of syncope with associated bundle branch block are reported. These cases were of four types. (1) Persistent bundle branch block and complete A-V heart block. (2) Tran-

sient bundle branch block and complete A-V heart block, which were observed only during periods of syncope, the electrocardiogram being normal in the intervals between attacks. (3) Delayed A-V conduction with transient incomplete A-V block and bundle branch block. (4) Permanent bundle branch block with normal A-V conduction during the intervals between syncopal attacks. Of this last type, there were twelve cases; and in ten of these, the electrocardiogram was recorded during syncope and showed complete A-V heart block. In the majority of cases, death occurred within a few months or years after the onset of the syndrome. It is pointed out that in cases of normal rhythm with bundle branch block the occurrence of syncope is often attributable to a paroxysmal Stokes-Adams attack. Within a few months or years, the patient either dies or a permanent complete A-V heart block occurs.

LAPLACE.

Van Bogaert, A., and Van Genabeek, A.: Contribution to the Study of Electrocardiographic Abnormalities of the P-Q Interval. Cardiologia **11**:255, 1946-47.

Two patients are presented who showed a second positive deflection (designated the X wave) after the P wave. The X wave closely resembled the P wave and followed it immediately. In the first case the X wave originated in Lead II from the isoelectric line immediately after P and had the same amplitude, but its descending limb was amputated in its middle by the ascending limb of R. After ten days of thyroid medication for postoperative myxedema it was evident that the X wave was actually the initial premature deflection of R, characteristic of the Wolff-Parkinson-White syndrome (W-P-W). In the second case, X was clearly visible in Leads I and II, but was of less constant amplitude. It originated below the isoelectric level, became positive, and finally continued on the isoelectric line with the ascending limb of R. Thus a Q wave was formed. This picture appeared shortly after an anterior wall infarct.

Without rejecting all the theories offered to explain the W-P-W syndrome, the authors suggest that the shortening of the P-Q interval and the lengthening of the QRS complex are only apparent and are the result of a supplementary X wave superimposed on the end of P-Q and the beginning of R. The X wave may be of auricular or ventricular origin.

The authors further point out that interference with the QRS-T complex by a slow auricular T wave can reproduce and explain all the known forms of the W-P-W syndrome. Depending on the amplitude, direction, and time relation of T_a with QRS-T, a simple Q wave, a descending staircase picture, or the minor forms of the W-P-W syndrome may appear. These anomalies of T_a are the expression of hyperexcitability of the auricular myocardium, which is manifested also by paroxysmal tachycardia and flutter or fibrillation. The cause may be anatomic or functional (coronary sclerosis, neurovegetative imbalance). The authors express their opinion that hearts with such manifestations cannot be considered normal in spite of the absence of other objective findings. Whatever causes the hyperexcitability may eventually cause a depression. Thus, diminished sinoauricular conduction, retarded sinonodal conduction, or shift of the pacemaker may result in shortening of the P-Q interval.

The previously mentioned anatomic and functional conditions may also cause hyperexcitability of the ventricular conduction system. A true shortening of P-Q results when the Tawara node is hyperexcitable. If one of the branches of the bundle of His is more excitable than the other, QRS occurs prematurely and P-Q is only apparently shortened. The proof of such origin is the persistence of the typical complex after suppression of auricular activity. In each case the changes after the initiation of the carotid sinus or oculocardiac reflex should be observed to determine the role of the auricle and the ventricle in the production of the syndrome.

The authors consider that the persistence in some cases of embryologic remnants of the auriculoventricular junction must be accepted with great reserve since no indication of their function exists in vivo.

LENEL.

Thordarson, O.: Clinical Studies on the Relative Incidence of Congenital Heart Disease. Acta med. Scandinav. **127**:233 (No. III-IV), 1947.

The difficulties of estimating accurately the incidence of congenital heart disease are discussed and the relevant literature reviewed. The author found that of 31,771 hospital admissions

0.27 per cent had congenital heart lesions, or 1.8 per cent of those who had heart disease. Three-fourths of these patients had not been cyanosed or seriously hampered by their congenital heart lesions. The salient findings in eighty-four cases examined by the author are tabulated and the significance of various clinical symptoms discussed.

SAYEN.

Nylin, G., and Biorck, G.: Circulatory Corpuscle and Blood Volume in a Case of Patent Ductus Arteriosus Before and After Ligation. Acta med. Scandinav. **127**:434 (No. V), 1947.

Study of the circulating blood volume by the radiophosphorus method for "tagging" red blood corpuscles (de Hevesy) confirmed previous observations by other workers, using the blue azo-dye technique, that there was a decrease after ligation of a patent ductus arteriosus. The red cell count decreased 8 per cent; the circulating blood volume, 12 per cent; and the roentgenographic heart volume, 19 per cent. The authors feel that their study supports the view that the blood volume is increased in shunts of the ductus arteriosus type.

SAYEN.

Espersen, T., and Jorgensen, J.: Electrocardiographic Changes in Paroxysmal Hypertension Due to Chromaffin Adrenal Tumor. Acta med. Scandinav. **127**:494 (No. V), 1947.

The electrocardiographic findings in a case of paroxysmal hypertension due to pheochromocytoma of the adrenal and associated with thyroid hyperplasia are presented and discussed. Between attacks, tracings were normal or showed sinus tachycardia, auricular fibrillation, flutter, or sinoauricular block. Three tracings recorded during attacks of hypertension, headache, and palpitation showed auricular fibrillation with many deformed ventricular complexes in two instances, while on the third occasion atrioventricular dissociation was observed. Postoperatively, one tracing showed auricular fibrillation and subsequent recordings were normal. The Q-T segment and T-wave changes reported by other writers were not seen.

The authors concur with the view of others that the alterations in rhythm are produced by increased epinephrine content of the blood through "combined accelerans and vagus effect, the latter via the pressosensitive zones." They believe that the peculiarly characteristic electrocardiographic abnormality associated with pheochromocytoma is heterotopic stimulus formation, and that T-wave alternation, described by others, is probably associated with hypertension rather hyperepinephrinemia.

SAYEN.

Djin-Yuan Guo: Dissecting Aneurysm of the Aorta Related to Trauma. Acta radiol. **28**:25 (No. I), 1947.

After citing instances of posttraumatic dissecting aneurysm from the medical literature, including three asymptomatic cases, the author reports the case of a 39-year-old farmer who fell off a horse in 1935, struck his chest on a stump, and fractured his sternum and some ribs. He recovered after "bilateral pneumonia." X-rays taken then (1935) showed a "double" aortic knob which was of similar appearance in 1944, save for calcification in part of the wall. In the oblique projection the calcified transverse and descending aorta could be seen to form a "camel's hump," a double angulation with a downward-bowed connecting link replacing the smooth curve of the aortic arch. The patient himself felt well and continued an athletic existence.

The rare but occasional occurrence of painless dissecting aneurysm of the aorta after trauma is emphasized as a possibility not often enough investigated by roentgenography in cases with clinical diagnoses of cardiac concussion.

SAYEN.

Lindgren, A.: Cutaneous Precordial Anaesthesia in Angina Pectoris and Coronary Occlusion (an Experimental Study). Cardiologia **11**:207, 1947.

Sixteen patients with the anginal syndrome were subjected to hypoxemia (breathing of a 10 per cent oxygen, 90 per cent nitrogen mixture) until angina occurred. The time of appearance

of pain was noted and the area of pain was mapped out on the skin. Electrocardiograms were taken at frequent intervals before, during, and after the test. The capillary oxygen saturation was also determined. The mapped out skin area was anesthetized by subcutaneous injection of 1 per cent novocaine without epinephrine. Most patients tolerated the hypoxemia longer after the anesthesia and the pain was less severe. In some patients the pain "migrated" outside the anesthetized area. In fourteen patients the electrocardiogram improved after anesthesia.

Eleven patients were made to exercise by bicycle until the appearance of pain. After anesthesia, with the same amount of work, seven patients remained free from pain and two were much improved. Nine showed significant improvement of the electrocardiogram. Two patients had relief of pain without change in the electrocardiogram. Two patients were anesthetized during spontaneous attacks of angina, after the recording of an electrocardiogram. Following the infiltration of the skin, the electrocardiographic changes and the pain disappeared.

The authors speculate whether their results signify improved coronary circulation, and whether cervicothoracic sympathectomy achieves the same results. Two patients subjected to the hypoxemia test before and after the operation experienced greatly reduced discomfort and milder electrocardiographic changes.

Five patients with acute myocardial infarction were anesthetized with LL30 (effective for five to six hours). The severe pain disappeared, leaving a sensation of dull substernal oppression. The pain reappeared but was less severe after the anesthesia wore off. The electrocardiographic changes were not affected.

LENEL.

Libbrecht, L., A Special Form of Essential Hypertension With Paradoxical Pharmacodynamic Reactions. Acta clin. belg. **2**:106 (Jan.-Feb.), 1947.

A syndrome of essential hypertension is described in which the subcutaneous injection of 1.0 mg. of adrenalin is followed by paradoxical hypotension with bradycardia and paradoxical leucopenia with lymphopenia. Subcutaneous injection of atropine produces paradoxical stimulation of the gastric secretion. Reversal of the paradoxical reaction to adrenalin is produced by a preventive injection of atropine.

The probable mechanism and etiology of the paradoxical reactions are discussed. The author believes that a state of hypoparasympathicotonia is the basis of the syndrome for which he proposes the name "neurotonic hypertension."

LAPLACE.

Gobat, P. Y.: Variations of the Amount of Cytochrome-C in the Myocardium and in the Striated Muscle in Human Pathology. Helvet med. acta **14**:45 (Feb.), 1947.

The following is a report of a study of the cytochrome-C levels in skeletal and heart muscle under normal and various pathologic states.

The cytochrome-C level of muscle is subject to individual variations. The myocardium, however, always contains more respiratory pigments than skeletal muscle. This difference is accentuated with age, and can be recognized very distinctly by an increase of the relation between cardiac and muscular cytochrome or C/M. This increased from 2.93 mg. per cent, between the ages of 20-30 years, to 3.77 mg. per cent, between 80-90 years, with its minimum between 50-60 years. This increase of the C/M results especially from a pronounced diminution of muscular cytochrome in old persons. However, cardiac muscle has a more or less constant requirement of catalysts for its cellular respiration. Hypertension causes an increase of heart respiratory pigments in relation to the muscular hypertrophy.

Children have only a small amount of cytochrome. But later in life the muscle fiber is rapidly enriched in cytochrome-C and contains the greatest amount between 20 to 30 years. Beyond this age, a tendency of progressive decrease can be observed in spite of the fact that a slight increase can be seen in persons from 50 to 60 years of age.

Diseases involving the whole body have a similar influence upon both cardiac and muscular cytochrome and the relation C/M presents an increase according to age both in sick and in healthy persons. Acute infections and even acute febrile infectious diseases possess hardly any influence

on the cytochrome level; whereas chronic diseases exert a very marked effect, especially infections with febrile courses, for example, tuberculosis which exerts an especially marked action.

In acute febrile infectious diseases this loss is certainly more pronounced, but cytochrome-C metabolism is a relatively slow process and the variations of the cytochrome level can be seen only after two to three weeks. Cancer also causes a diminution of the cytochrome level. In diabetes, the cytochrome level is sometimes reduced, whereas cases of uremia are accompanied by an augmentation of the respiratory pigments. Local alterations in the heart muscle can also modify the level of cellular respiratory catalysts and there is a distinct decrease of cardiac cytochrome in cases of myocarditis, fibrous and fatty degeneration of the myocardium, and coronary stenosis, whereas just the contrary can be seen in cases of arterial hypertension accompanied by hypertrophy of the heart muscle.

BELLET.

Chesley, L. C., and Annitto, J. E.: Pregnancy in the Patient With Hypertensive Disease. Am. J. Obst. & Gynec. **53:**372 (March), 1947.

In a statistical analysis of 301 pregnancies in 218 patients whose histories established a diagnosis of "hypertensive toxemia" as defined by the American Committee on Maternal Welfare, the dangers of pregnancy in the hypertensive patient are clearly pictured. Only cases were included known to be hypertensive prior to pregnancy or in whom the diagnosis was made in the first twenty-four weeks. The standard for hypertension was taken as 140/90.

The frequency of Negro patients in the hypertensive group was more than twice that in total hospital admissions. In general, proteinuria varied directly with the degree of hypertension, though at least three-fourths of the patients were considered to have normal renal function. Pre-eclampsia was a complicating factor in 30 per cent of these cases. No clear-cut relation between the development of toxemia and the prepregnant or first trimester blood pressure could be made. Seventy-one per cent of hypertensive patients developing toxemia of pregnancy may be expected to have a recurrence in future pregnancies.

The hazards to the pregnant hypertensive are not great in two-thirds of the cases, but unfortunately the development of future pre-eclampsia or eclampsia cannot be predicted easily in a given case. The total maternal mortality in this group was twenty times that for the whole hospital experience, the fetal loss was ten times, and the incidence of toxemia was seven times that of the normal controls.

The mid trimester drop in blood pressure was of some diagnostic importance. If not recognized as such, the acute rise to be expected after the twenty-fourth week would lead in many cases to an erroneous diagnosis of pre-eclampsia. Further, a mid pregnancy rise in pressure was found to be ominous for future fetal prognosis.

KERN.

Sobin, S. S., and Landis, E. M.: Blood Pressure of the Rat During Acute and Chronic Choline Deficiency. Am. J. Physiol. **148:**557 (March), 1947.

In view of the renal damage involving glomeruli which can be produced by diets deficient in choline, the authors attempted to study this deficiency in relation to hypertension. Male weanling rats were used. In acute choline deficiency, only six of eighteen rats survived, a mortality of 66 per cent. All the survivors had enlarged kidneys during the period of illness. However, there was no significant change in blood pressure.

Weanling male and female rats were used in the chronic experiments. At the end of five months, the systolic blood pressures of the choline deficient animals and the control group were the same. Therefore, in spite of the fact that the renal damage produced by choline deficiency persists for months and involves glomeruli as well as tubules, there is no hypertension produced. This suggests that the renal lesions resemble those of the nephroses.

BERNSTEIN.

Eckenhoff, J. E., Hafkenschiel, J. H., and Landmesser, C. M.: The Coronary Circulation in the Dog. Am. J. Physiol. **148**:582 (March), 1947.

In these experiments the coronary blood flow was measured by the bubble flow-meter which was so inserted that one end was in the coronary artery to be studied and the other end in the carotid artery.

With this method, the so-called "normal" coronary flow was 65 c.c. per 100 grams of heart per minute. This figure varied little when the chest was either open or closed. Coronary flow is directly related to the mean arterial blood pressure with a fall in coronary blood flow with falls in blood pressure. Heart rate acceleration also increased coronary blood flow. Stimulation of of the vagus or accelerator nerves had no significant coronary vasoconstrictor effect. Stimulation of the accelerator nerves did increase coronary flow, but usually only when blood pressure and heart rate also rose. In a few cases, however, there was acceleration of flow even without these changes. Stimulation of the vagus produced changes in coronary blood flow only when there were blood pressure or heart rate changes. Following atropine, stimulation of the vagus did not cause a reduction in coronary blood flow.

Ligation of one coronary artery caused no reflex vasoconstriction in five experiments. When the blood pressure began to fall, however, the flow began to decrease. Increasing the intrabiliary tension caused variable changes in the coronary flow, but they were always in the same direction as blood pressure change. Repeating the experiment after atropine, the changes of flow, blood pressure, and heart rate were not so marked.

In small doses, acetylcholine intraarterially increased the rate of flow. In larger doses, the increased flow was followed by a slowing. After atropine, acetylcholine was ineffective. Acetylcholine injected intravenously decreased coronary flow, probably due to the accompanying hypotension. Epinephrine increased coronary blood flow without significant change in heart rate or blood pressure, suggesting that this drug has a dilator effect upon the coronary arteries in small doses. In large doses its effect is probably due to increased cardiac metabolism.

It was found that the fraction of the cardiac output passing through the coronary arteries varies inversely with the cardiac output, so that under standard conditions the coronary arteries receive 4 to 5 per cent of the total cardiac output; but when the cardiac output fell to 500 c.c. or less per minute, more than 9 per cent of the total flowed through the heart. However, the actual flow per 100 grams of heart usually decreased as the output fell.

Coronary vessels are dilated by accumulated products of local metabolism. One hundred per cent oxygen decreased the rate of coronary blood flow. Carbon dioxide caused no consistent alteration in coronary flow when 5 to 7 per cent was used. Lowering of the blood pH caused no decrease in coronary flow, even though there was a drop in blood pressure.

BERNSTEIN.

Bruner, H. D., and Schmidt, Carl F.: Blood Flow in the Bronchial Artery of the Anesthetized Dog. Am. J. Physiol. **148**:648 (March), 1947.

Bronchial artery flow was measured by the bubble flow-meter in fifty anesthetized dogs, in order to evaluate the role of bronchial artery flow in the etiology of paroxysmal and other types of pulmonary edema. Using P^{32}, blood flow was measured and it was found that 69 per cent of the blood flow through the right bronchial artery goes to the right lung and 31 per cent to the mediastinal structures. From this, they found that a factor of 1.26 times the observed right bronchial flow would approximate the total flow discharged into the pulmonary veins in a given dog per minute. Blood flow was highest during the beginning of the experiment and decreased with time. It appeared to be more closely related to cardiac output than to any other factors. The average flow was 0.3 per cent of cardiac output. The maximal flow was 2.0 to 2.5 times the average normal flow. They estimate that 30 to 40 c.c. per minute is the maximum total drainage into the pulmonary veins from both right and left bronchial arteries. This is about 1.25 per cent of the entire cardiac output and is considered to be insufficient to embarrass the drainage capacity of the pulmonary veins.

There was much spontaneous variation of bronchial blood flow. These changes were not related to blood pressure, spontaneous or pump ventilation, bilateral vagotomy, anesthesia, hem-

orrhage, or the amount of oxygen present, or movements of the larynx, esophagus, or other parts of the body. The source of the variations, therefore, appeared to be in the bronchial arteries themselves. The artery is dilated by fibers in the vagus and constricted by fibers in the accelerator nerve. However, two exceptions suggested the possibility that the accelerator nerve fibers are not exclusively constrictor. On the whole, however, the vagus is cholinergic and the accelerator essentially adrenergic. Response of this artery to drugs and abnormal oxygen and carbon dioxide tensions was much like that of other systemic arteries. From this data, it seems unlikely that increases in bronchial artery flow could overtax the drainage capacity of the pulmonary veins and raise pulmonary capillary pressure.

The distinctive feature of bronchial artery circulation seems to be its spontaneous variability. From a vasomotor innervation point of view it acts more like the splanchnic and periperal arteries than the cerebral and coronary vessels. From the data, it would seem that bronchial flow to a given sector of lung would be so small as to inadequately maintain the alveolar structure in an area where pulmonary artery flow has been blocked or severely restricted. However, because the alveoli are independent of blood flow for their gaseous metabolic requirements, this small flow may be ample.

BERNSTEIN.

Opdyke, David F., and Foreman, Robert C.: A Study of Coronary Flow Under Conditions of Hemorrhagic Hypotension and Shock. Am. J. Physiol. **148**:726 (March), 1947.

The authors used an optical recording flow-meter of the perfusion type in which the rate of pressure decline within the meter is nearly proportional to the rate of inflow into the bed. This flow-meter is similar to that described by Green and Gregg, but differs in the method of operation. Control studies showed that coronary flow remained surprisingly consistent even with variations in blood pressure. Experiments showed that during the period of hypotension after hemorrhage the coronary flow is seriously curtailed. Immediately following reinfusion, and for some period thereafter, coronary blood flow is greater than during the control period, in spite of the fact that mean aortic pressure is slightly less than during the control period. Actual coronary flow is greater during shock than at similar levels of blood pressure in the preshock state.

This led the authors to conclude that there are no mechanisms operating which tend to reduce actual coronary flow other than loss of pressure head due to the decline of mean aortic pressure. Further, resistance to flow in the shock state is always less than control. Further, an inadequate coronary flow is not responsible for the circulatory failure following transfusion. It would appear, therefore, that myocardial damage in shock must come from a direct metabolic disturbance in the cells of the myocardium, resulting from the reduced coronary flow during the hemorrhagic hypotension period.

BERNSTEIN.

Eckstein, R. W., Wiggers, C. J., and Graham, G. R.: Phasic Changes in Inferior Cava Flow of Intravascular Origin. Am. J. Physiol. **148**:740 (March), 1947.

The authors measured the pressure changes in the inferior vena cava by using a modified Pitot cannula. This cannula was provided with a small baffle plate on the afferent side and the tube on the efferent side was so placed as to transmit the pressure at the point of maximum blood velocity. This double tube was so adjusted that it did not interfere with natural flow as detected by rise of pressure in the abdominal inferior cava. Using this technique, it was found that the rhythmic fluctuations in flow in the inferior vena cava were proportional to the changes caused by systole and diastole in the auricle of the heart. Observation of the effect of diaphragmatic excursions showed that descent of the diaphragm increased the basic flow through the inferior vena cava significantly after a slight reduction at the beginning of descent. This effect occurred even after hemorrhage.

BERNSTEIN.

Casman, J.: Radiographic Demonstration of the Increase in Heart Volume After Ingestion of a Litre of Water. Acta. clin. belg. **2**:113 (March-April), 1947.

Enlargement of the heart in persons who are heavy beer drinkers has been attributed to hydremia and to hypertension. An additional cause was suggested by Govaerts and Lequime, who found that drinking a liter of water was followed by an average of 20 per cent increase in the work of the heart. The possibility that the increased work is accompanied by enlargement of the heart was investigated by the author.

Twenty subjects, selected at random from a radiologic outpatient department, were studied. An x-ray film of the chest in the frontal plane was made before and forty minutes after drinking 1.0 liter of water. The duration of exposure included a complete cardiac cycle so that the cardiac silhouette could be measured in diastole. The measurements of three diameters were recorded: transverse, upper left to lower right border, and upper right to lower left border. After drinking the liter of water, these diameters were found to be increased by 5.31, 4.84, and 4.11 per cent, respectively. If the heart were spherical, an increase of 5 per cent in the diameters would indicate an increase of 15 per cent in the heart volume; when the increase in the diameters was maximum (10 per cent), the increase in heart voume would be 33 per cent.

It is concluded that when absorption of liquid is excessive, it may lead to the marked cardiac enlargement which characterizes the "beer heart."

LAPLACE.

Marshall, F. A.: Tetany Following Mercurial Diuresis. J. A. M. A. **133**:1007 (April 5), 1947.

The author presents the case of a 60-year-old woman who had been treated over a period of five months for congestive failure by digitoxin and repeated mercurial intramuscular injections. The patient suffered recurrent episodes of congestive failure and nocturnal dyspnea, and had been vomiting in spells. During one of these attacks of failure, the calcium was 7.4 mg. and phosphorus, 5.5 mg. per 100 cubic centimeters. Mercurial diuretics (mersalyl and mercurphylline injections chiefly) had been given at intervals of three to ten days as required by edema and congestive failure.

On three separate occasions, tetany followed the parenteral use of mercurial diuretics. The author stresses the need for thought on the mobilization and excretion of electrolytes other than the chlorides. Relief was obtained through the use of parenteral and oral calcium. It appears that tetany is more likely in patients who ordinarily have a borderline calcium deficiency, which is further reduced below this critical level by excessive diuresis.

BELLET.

Krieger, V. I., and Weiden, S.: The Value of the Cold Pressor Test in the Prediction of Hypertension and Toxemia in Pregnancy. Med. J. Australia **1**:417 (April 5), 1947.

The authors report that in a series of 522 cold pressor tests performed during 200 pregnancies, all tests gave normal results in eighty-four instances; hyper-reaction to the cold stimulus occurred in one test only on each of thirty-one patients, and in more than one test on each of eighty-five patients. Of all patients whose cold pressor tests gave normal results, only thirteen developed hypertension in the later stages of their pregnancies. In four of these patients the hypertension was associated with pre-eclampsia. In those patients in whom only one test gave a result of the hyper-reactive type, half had a normal pregnancy; the other half developed either hypertensive toxemia or pre-eclampsia. When mild hyper-reaction occurred on more than one occasion, twenty-six of the eighty-five patients had a normal pregnancy, but forty-nine developed hypertensive toxemia, and ten had pre-eclampsia. In the hands of the authors, the cold pressor test has given consistent results throughout pregnancy in the majority of their cases, and erratic results have been the exception.

The results of cold pressor tests performed two and twelve months after delivery are valuable in assessing the prognosis of subsequent pregnancies. Those patients who still show hyper-reaction twelve months after delivery should probably be classified as hypertensive. In the cases in which the hyper-reaction response is replaced by a normal response some time after delivery,

it can be assumed that the abnormal response during the pregnancy was caused by some specific agent which may not be active in a subsequent pregnancy.

The authors feel that the results of serial cold pressor tests during pregnancy are of value to the obstetrician, since, even if only one response in the series is of the hyper-reactive type, 50 per cent of the patients giving such responses develop hypertensive or pre-eclamptic toxemia. When two or more abnormal results are obtained, the number of patients who develop such toxemia increases to nearly 70 per cent. On the other hand, toxemia occurs later in the pregnancy in only a few patients in whom the response to the test is always normal.

Follow-up tests two and twelve months after delivery are sometimes helpful in assessing the prognosis of subsequent pregnancies, since patients who have hypertension, or are likely to develop it, can be differentiated from those unlikely to have this complication.

BELLET.

Bartholomew, R. A.: The Possible Etiologic Significance of Thrombosis of a Placental Vein on the Mechanism of Placental Infarction and Associated Toxemia of Pregnancy. Am. J. Obst. & Gynec. 53:650 (April), 1947.

In a case of acute fulminating toxemia developing at term in a 28-year-old nullipara, pathologic examination of the placenta showed thrombosis of a vein on the fetal surface with an associated broad area of plainly demarcated acute infarction. The author advances the belief that such thrombosis was causative of the subsequent acute toxemia, arguing that placental tissue has been shown to possess a high content of arginine together with arginase, an enzyme theoretically capable of producing guanidine, a known eclamptogen. Thus, hypothetically, autolysis of necrotic villi produced by such thrombosis could result in the dissemination of poisonous protein split-products into the maternal circulation with widespread damage to liver and kidneys which could provoke an ultimate eclamptic state.

KERN.

Wastl, H.: Observations of Influence of Corn-Silk Extract (Stigmata Maydis Zeae) on Blood Pressure in Hypertensive Rats. Arch. Internat. de pharmacodyn. et de thérap. 74:1 (April), 1947.

The author studied the influence of injections of corn-silk extract (Stigmata maydis zeae) on the blood pressure of rats rendered hypertensive by looping a stout cotton thread over the poles of both kidneys (method of Grollman and Harrison). One c.c. per 100 Gm. of rat, or 0.1 mg./kg. of corn-silk extract in aqueous solution, 1.10^{5} concentration, was injected intraperitoneally and its effects studied. The hypertensive rats were divided into three subgroups; rats with slight hypertension (0 to 20 per cent), rats with medium hypertension (plus 20 per cent to plus 40 per cent), and rats with marked hypertension (over plus 40 per cent). The percentage figures represent the permanent increase over the respective individual normal blood pressures. Pretreatment observations were followed by four consecutive days of injections and then wound up by four consecutive days of posttreatment observations.

No significant influence on the blood pressures of normotensive rats was observed. Hypertensive animals, however, responded with a moderate reduction of blood pressure. The average declined by 15.0, 13.2, and 12.8 mm. Hg in the slight, medium, and marked hypertension groups, respectively. A return to the preinjection pressure level was complete on the second day after cessation of the injection. No adverse effect whatsoever was observed.

The most favorable results as regards decreases of the levels of systolic blood pressures, were achieved with the combination of hydrobromide paredrine and with S-Benzyl-iso-thiourea-hydrochloride. Somewhat less effective is a second pair, corn-silk extract and S-Methyl-isothiourea sulphate. The present report, dealing with corn-silk extract, shows that it has certain possibilities in the alleviation of human hypertension.

BELLET.

Kelly, H. G., Gibson, W. C., and Meakins, J. F.: Cerebral Air Embolism Following Artificial Pneumothroax Treatment With Prolonged Inhalation of Oxygen. Canad. M. A. J. **56**:388 (April), 1947.

A 28-year-old woman who had been suffering from bilateral apical tuberculosis was given a routine pneumothorax refill. As the needle was withdrawn the patient went into a violent convulsion. These seizures recurred at short intervals for a period of three hours. On the following day she was still in deep coma but was breathing regularly and freely. The left extremities were unresponsive and lifeless. Treatment with a mixture of carbon dioxide and oxygen, and later 100 per cent oxygen, resulted in gradual improvement with return of consciousness. Residual apathy, drowsiness, and confusion gradually disappeared. Six days after the preceding episode, the patient was well.

Electroencephalograms obtained over a period of six months showed obliteration of normal cortical activity, which gradually returned toward normal.

BELLET.

Rees, H. C., and Slevin, J. G.: Surgical Management of Vascular Leg Ulcers. Surgery **21**:575 (April), 1947.

The authors discuss the various procedures utilized in the treatment of ischemic and varicose ulcers. With regard to local therapy the first aim is to combat infection, a frequent complication. For this purpose, the authors have found a solution of gentian violet painted on the ulcer, combined with a light dusting with sulfathiazole crystals, to be quite effective. The systemic use of sulfonamide compounds has not been found to be as efficacious as their local application because the local blood supply is generally impaired. However, prolonged topical use of these substances will inhibit epithelization. Another procedure which has certain advantages over the local use of sulfonamides is a new soluble dressing containing a nitrofuran compound. After infection is controlled, the authors have found that pressure dressings, in the form of soft sponged rubber, applied to the ulcer site and held in place by a cotton elastic bandage helped to hasten the healing of the lesion. In those instances in which the etiological factor is a varix feeding the involved site, the affected veins should be ligated, with subsequent injection of any remaining varicosities with a sclerosing solution. This step should be delayed until infection is under control.

In those instances in which the ulcer persists after adequate treatment, other causes should be sought, such as arteriosclerosis obliterans or the presence of scar tissue surrounding the ulcer and interfering with the local blood supply. In case dense scar tissue is present, it may be necessary to resort to plastic operations on the ulcer, consisting of an eliptical incision around the ulcer including the margin of scar tissue. The incision is carried down to the deep fascia. The wound is allowed to form healthy granulations which are subsequently skin grafted. In most instances such an extensive plastic operation is not necessary, and healing can be brought about with skin grafting alone. This procedure not only lessens the period of disability by weeks but also affords the best insurance against recurrence. The most successful skin graft method, according to the authors, is the pinch graft type. When dealing with leg ulcers in patients with a history of an old deep phlebothrombosis, the results with the usual procedures are generally poor. The authors have found that in such instances ligation of the femoral vein below the profunda and also the saphenous veins improves the circulation and permits successful skin grafting of the ulcer site.

ABRAMSON.

Parker, R. L., and Barker, N. W.: The Use of Anticoagulants in the Management of Acute Myocardial Infarction: A Preliminary Report. Proc. Staff Meet., Mayo Clin. **22**:185 (May 14), 1947.

The use of dicumarol and heparin in the management of acute coronary thrombosis with myocardial infarction is based on four principal objectives: (1) prevention of an extension of the thrombus; (2) prevention of the formation of intracardiac mural thrombi; (3) prevention of thrombophlebitis from which pulmonary embolism may arise; and (4) prevention of thrombosis

in peripheral arteries already considerably affected by arteriosclerosis. The purpose of this preliminary report is to present the authors' experience in the first fifty cases of acute myocardial infarction in which these preparations were used. The series of 100 cases reported by Nay and Barnes is used as a control series.

In ten cases, heparin was used in combination with dicumarol; in forty cases, dicumarol was used alone. When heparin is employed, an immediate anticoagulant effect is obtained. When dicumarol is used alone, there usually is a lapse of approximately thirty-six to forty-eight hours before the prothrombin level is reduced sufficiently to prevent intravascular clotting. Twenty patients in this series obtained an adequate anticoagulant effect within forty-eight hours after the onset of acute myocardial infarction. In eighteen cases a period of two to five days elapsed before an adequate effect was obtained and in twelve cases there was a lapse of more than five days. In no instance was a serious complication encountered as the result of anticoagulant therapy.

Two patients in this series of fifty cases had secondary vascular complications while they were receiving anticoagulant therapy during their convalescent period in the hospital, in comparison with 37 per cent of the patients who had such complications in the control series in which anticoagulants were not used. The difference in the mortality rate in respect to patients treated with anticoagulants and those not so treated was not notably different: 10 per cent and 13 per cent, respectively. It would seem, therefore, that although there was a marked reduction in the incidence of thromboembolic complications among the patients who received anticoagulant therapy, there was little influence on the total mortality rate.

BELLET.

Chesley, L. C., Annitto, J. E., and Jarvis, D. G.: A Study of the Inter-Action of Pregnancy and Hypertensive Disease. Am. J. Obst. & Gynec. 53:851 (May), 1947.

In a continuing study of 301 pregnancies in 218 patients with hypertension, an attempt was made to determine the effect of pregnancy on hypertensive disease. The study showed that the majority (66 per cent) of hypertensive women apparently were not jeopardized by pregnancy, though in the one-third that did not escape superimposed toxemia, the incidence of maternal and fetal mortality was greatly increased over that of the whole hospital experience. Of the total 218 cases acurately followed up to 1946, 17.9 per cent were dead; of the one-third who developed superimposed toxemia along with their hypertension, 31.7 per cent were dead; of the remaining two-thirds who did escape superimposed toxemia only 9.6 per cent were dead.

Statistical analysis and clinical study of this carefully followed group of patients led the authors to conclude that repeated pregnancies are not demonstrably harmful to the hypertensive woman, though pregnancy itself is hazardous should toxemia occur.

KERN.

Davis, M. E., and Wortmann, R. F.: Subacute Bacterial Endocarditis During Pregnancy. Am. J. Obst. & Gynec. 53:878 (May), 1947.

Following a protracted sore throat in the thirty-second week of her third pregnancy, a 31-year-old woman was admitted to a hospital for study. The heart was found to be 40 per cent oversize by x-ray. Other positive findings were a loud, harsh heart murmur replacing the first sound at the apex and an abnormal patency of the eustachian tubes. Three weeks later the heart size had increased to 60 per cent above normal and repeated blood cultures were positive for *Streptococcus viridans*. During a course of thirty-six days, 45,850,000 units of penicillin were administered together with repeated small blood transfusions. Following the subsidence of the acute infection, a cesarean hysterectomy was performed in the thirty-eighth week of pregnancy because of two previous sections for cephalopelvic disproportion and to decrease the hazard of postoperative infection. Recovery was uneventful, the patient being discharged on her forty-fifth postoperative day with repeated negative arterial and venous blood cultures, a normal white count, and a near-normal sedimentation rate. During the subsequent year there was no recurrence of the subacute endocarditis, though the heart remained enlarged and showed findings typical of mitral disease. The spectacular recovery did not forestall serious residual cardiac damage.

KERN.

Honigman, A. H., and Karns, J. R.: Healed Subacute Bacterial Endocarditis: Report of Two Cases With Death Due to Congestive Heart Failure. Ann. Int. Med. **26**:704 (May), 1947.

Two patients having subacute bacterial endocarditis, in whom the diagnosis was confirmed by the recovery of *Streptococcus viridans* from the blood stream, ultimately succumbed to congestive heart failure even though all clinical and laboratory evidences of persisting infection were eradicated by adequate amounts of penicillin. Autopsy examination was made in one of the cases. This revealed thickening of the free margins and adherence of the commisural portions of the aortic valve cusps, thickening and nodularity of the mitral valve, and tiny grape-like clusters of densely scarred calcified material on one of the adjoining chordae tendineae. Histologic study of these calcified nodules showed their structure to consist of dense scar tissue, traversed by endothelial and thick walled vessels, and extensive deposits of calcareous material. In various sections made through these fibrocalcareous vegetations, organisms could not be demonstrated by hematoxylin and eosin stain or Glynn's stain for bacteria.

WENDKOS.

Weintraub, H. J., and Bishop, L. F.: The Anoxemia Test for Coronary Insufficiency. Ann. Int. Med. **26**:741 (May), 1947.

The anoxemia test was employed for the study of patients with and without stigmata of coronary artery disease. The former group consisted of twenty adults who suffered from angina of effort and most of whose electrocardiograms were significantly abnormal, while the latter group, who were used as controls, included 200 patients who did not suffer from angina of effort even though fourteen of this number had various types of cardiovascular abnormality. The criteria of a "positive test" were those which had previously been established by Levy and co-workers.

As advocated by Levy, the test was not performed soon after the ingestion of food, in the presence of congestive heart failure, or within four months after known cardiac infarction. Repeat tests were never done on the same patient. If chest pain resulted during the test, it was discontinued and 100 per cent oxygen was immediately administered. In spite of these precautions, untoward effects were encountered not infrequently, both in the control group and in those exhibiting angina of effort. In a quantitative sense, there were 108 slight, thirty-seven moderate, and six severe reactions in the former group, and six slight, seven moderate, and two severe reactions in the latter group. In a qualitative sense, the reactions were quite variable. The most common symptoms were headache, dizziness, numbness, tingling, drowsiness, air hunger, and cyanosis. In the two instances in which twitchings of the extremities occurred, this symptom was abolished by the inhalation of 100 per cent oxygen. Chest pain also was relieved by similar means.

Of the twenty patients in whom a diagnosis of coronary artery disease seemed to be unequivocal prior to the performance of the test, eleven showed significant electrocardiographic changes following exposure to the low oxygen mixture. During the test, eight of these eleven cases, in addition, developed pain in the chest, six in less than ten minutes and two within ten to twenty minutes. In seven of the twenty patients with coronary disease, the electrocardiogram remained unchanged, but precordial pain appeared before twenty minutes of exposure. A negative electrocardiographic response and absence of pain were encountered in two of the twenty cases with coronary artery disease. Of the twenty patients with coronary artery disease, the control electrocardiogram was abnormal in thirteen instances. In eight of this latter group, electrocardiographic changes presumably indicative of transient myocardial ischemia developed. Analogous changes occurred in only three cases of the seven who had a normal control electrocardiogram.

In the 200 normal controls, the test did not provoke any chest pain. In this same group, electrocardiographic changes developed in nine. In seven of these nine cases, there were abnormal cardiovascular, hemic, or emotional factors present. In the other two of these nine cases no such factors were present.

Of the 191 normal controls who showed a negative electrocardiographic response, according to the criteria of Levy, there were twenty-three instances of T-wave changes primarily involving

the T waves in Leads I and IV and consisting of notching, a diphasic configuration, and flattening. No explanation for these minor T-wave changes is offered.

WENDKOS.

Stein, M. H., and Driscoll, R. E.: Paroxysmal Ventricular Tachycardia With Acute Left Ventricular Failure in a Patient With No Evidence of Organic Heart Disease. Ann. Int. Med. **26**:769 (May), 1947.

Following a drinking bout, an 18-year-old soldier developed an attack of sudden cardiac acceleration, chest pain, and moderate dyspnea for which he was immediately hospitalized. Similar attacks, lasting from ten minutes to ten hours and unrelated to alcohol, had recurred at variable intervals ever since the age of 5 years. These episodes always ceased spontaneously and did not result in any further disability. At the time of his hospital admission, the physical examination revealed a heart rate of 200 per minute with a regular rhythm. One hour following his admission, he suddenly developed an even greater cardiac acceleration associated with orthopnea, cyanosis, and cough productive of large amounts of bloody, frothy sputum. The examination at this time revealed the typical findings of pulmonary edema. Emergency treatment was given and an electrocardiogram made shortly thereafter showed the presence of what was interpreted to be ventricular tachycardia with a rate of 230 per minute. Twelve hours after admission, the paroxysm of tachycardia subsided and an electrocardiogram made then showed the presence of a sinus rhythm with a rate of 110 per minute and no changes in any of the auricular or ventricular deflections. The physical examination at that time revealed no abnormal findings. Repeated clinical examinations and laboratory studies of the heart were normal and failed to indicate any form of organic heart disease.

WENDKOS.

Reitman, N.: The Antistreptolysin Titer as a Diagnostic Aid in Carditis of Obscure Etiology. Ann. Int. Med. **26**:774 (May), 1947.

A 15-year-old schoolboy developed an acute febrile illness, during the course of which inconstant systolic basal and apical murmurs were audible. There were no joint pains, epistaxis, rash, or abdominal pain to suggest the diagnosis of acute rheumatic fever. An electrocardiogram at the beginning of the illness showed a bizarre disturbance of rhythm, which seemed to be the result of a wandering pacemaker, and frequent premature contractions. Because of these findings, a diagnosis of acute carditis of undetermined cause was made and prolonged bed rest was advised. Three days following the original record, another electrocardiogram was made which showed a normal sinus rhythm with a heart rate of 60 per minute and normal auriculoventricular conduction. Another tracing made two weeks later was essentially unchanged. Approximately one month following the onset of the illness, the cardiac murmurs had disappeared. Antistreptolysin titers during the period of observation rose significantly. Follow-up examination several years later revealed no signs of valvular heart disease. He served as a combat infantry soldier during World War II and suffered no disability during this military service. The author concluded that the rise in antistreptolysin titer, and conjunction with the disturbance of cardiac rhythm demonstrable in the electrocardiogram, and the temporary systolic murmurs establish the fact that the acute febrile illness, during which the above phenomena were encountered, was an episode of acute rheumatic fever. Furthermore on the basis of his experience with this case, the author suggests that antistreptolysin titer determinations may prove to be a useful diagnostic aid in other cases of acute carditis of obscure etiology.

WENDKOS.

Clark, J. H., Nelson, W., Lyons, C., Mayerson, H. S., and De Camp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient. Ann. Surg. **125**:618 (May), 1947.

The authors describe a syndrome consisting of weight loss, decreased blood volume, decreased blood proteins (including hemoglobin and plasma proteins), and increased interstitial

fluid volume and call it "chronic shock." The importance of a reduced blood volume is seen in the tendency for the chronically ill patient to go into shock during major surgical procedures. Reduced blood volume is readily correctable by whole blood transfusions.

Many surgical conditions may result in a state of chronic shock. Among the most important are the following: malignancies, especially of the gastrointestinal tract, chronic sepsis, and hepatic disease.

The authors present considerable data to show that the hematocrit and plasma protein determinations fail to reveal the underlying deficit in blood volume and hence total blood hemoglobin and total plasma proteins. They also demonstrate that total hemoglobin suffers more than total plasma protein in the chronically ill patient. Blood volume is correlated more closely with the percentage of weight lost from the normal for any given individual than with other methods of estimation, such as surface area, age, sex, and height.

Therapeutically, whole blood transfusions of 500 ml. to 1,000 ml. daily are the best means of preparing a chronically ill patient for a major surgical procedure. Amounts of blood from 1,500 ml. to 4,000 ml. may be necessary.

LORD.

Freeman, N. E.: Direct Measurement of Blood Pressure Within Arterial Aneurysms and Arteriovenous Fistulas. Surgery **21**:646 (May), 1947.

Freeman employed an aneroid manometer attached to a three-way stopcock, which in turn was connected to a 20-gauge needle and a 10 c.c. syringe. After the aneurysm or fistula had been exposed, the component vessels were controlled by means of rubber tubing. The end of the needle was then inserted into the aneurysm or fistula and the blood pressure noted. Additional readings were taken when the proximal artery and then the distal artery were occluded, and also when both vessels occluded. In cases with an arteriovenous fistula further studies were carried out with the vein occluded.

Twenty-three patients were studied. The mean initial pressure in the group with the arterial aneurysm averaged 84 mm. Hg with variation of 110 to 34 millimeters. When the afferent artery was occluded, the pressure fell to an average of 59 mm. of mercury. In the group of patients with arteriovenous fistulas, the mean initial pressure averaged 40 mm. Hg with variations between 70 and 30 millimeters. With constriction of the afferent artery the pressure fell to an average of 10 mm. of mercury. The author believes that the lowest safe mean arterial pressure after excision of an aneurysm or arteriovenous fistula is approximately 32 mm. of mercury.

Direct measurement of arterial pressures at the time of operative management is helpful in evaluating the adequacy of the collateral circulation.

LORD.

Shaffer, J. O.: A Method of Rapid Transfusion Into the Femoral Vessels In Patients Without Adequate Peripheral Superficial Veins. Surgery **21**:659 (May), 1947.

A relatively simple technique is described for inserting and immobilizing a number 20-gauge needle in the common femoral vein or femoral artery. Each needle is inserted vertically just below the inguinal ligament until its lumen is in the desired vessel, and held by 3 hemostats placed at right angles to the tube 120 degrees apart. The clamps are taped to the skin.

The method has great value when a patient is in need of blood or plasma and all of the superficial veins are occluded. In cases of profound shock the femoral artery is employed.

LORD.

Shaffer, J. O.: Intra-Arterial Penicillin in the Surgical Treatment of Infections of the Extremities. Surgery **21**:692 (May), 1947.

The author utilized intra-arterial injection of penicillin in local infections of the extremities, in order to obtain a higher concentration of the drug in the affected tissues than could be hoped to be reached by intravenous or intramuscular administration. With such a procedure, dilution of the penicillin is minimal, and at the same time the blood pressure forces the concentrated drug

into the local area supplied by the artery. The factor of increased capillary permeability, resulting from the inflammatory process, permits a greater filtration of the agent locally.

The technique of administration consisted first of producing vasodilatation of the vessels of the involved extremity, either by the subcutaneous injection of papaverine hydrochloride or by soaking the limb in a warm 1:9000 potassium permanganate solution for 20 minutes. A blood pressure cuff was placed around the extremity proximal to the infected portion and inflated to a pressure of 80 mm. Hg; and then the injection into the artery was made over a period of ten seconds, using a 20-gauge needle, 2 inches long. Routinely, a dosage of 50,000 units of penicillin in 10 c.c. of saline solution was given. The pressure in the cuff was maintained at 80 mm. Hg. for ten minutes after the termination of administration of the drug. Injections were given once or twice daily.

The author found that diabetic gangrene, and gangrene due to arteriosclerosis and frostbite with associated infection, osteomyelitis, suppurative joints, infected ulcerations of the legs and feet, and infected operative incisions all responded well to intra-arterial administration of penicillin. The procedure effectively overcame the difficulties offered by tissue barriers and vascular impairment which reduced the efficacy of penicillin administered intravenously or intramuscularly. As a result, various types of infection, with or without tissue necrosis, were effectively controlled, thus obviating surgery in many instances, simplifying it in some, and altering it from an emergency status to an elective procedure in others. Phlebothrombosis and infection at the site of injection were found to be contraindications to the use of intra-arterial administration of penicillin.

ABRAMSON.

Bauersfeld, S. R.: Dissecting Aneurysm of the Aorta: A Presentation of Fifteen Cases and a Review of the Recent Literature. Ann. Int. Med. **26**:873 (June), 1947.

The data available in the cases of fifteen patients having dissecting aneurysm, in all of whom the diagnosis was confirmed by necropsy, are presented. Hypertension was definitely known to exist in eight cases. A diastolic aortic murmur was noted in four instances. In five cases chest roentgenograms were made, and varying degrees of aortic widening were noted in three of this number. Electrocardiograms were made in four cases; in two of this number, depressed S-T segments in Leads II and III were noted but no correlation between these changes and the autopsy findings is made. In addition, the author includes an excellent discussion of the clinical features of dissecting aneurysm.

WENDKOS.

Baker, L. A., and Musgrave, D.: A Study of Mitral Stenosis in Patients Who Survived the Age of Fifty. Ann. Int. Med. **26**:901 (June), 1947.

The authors studied 106 patients with mitral stenosis, uncomplicated by other valvular lesions, who had lived beyond the age of 50 years. The diagnosis was based on the presence of a diastolic rumble at the apex. This was usually associated with an accentuated sharp first heart sound. Only thirty-two gave a definite history of antecedent rheumatic infection. Of this number, rheumatic fever occurred before the age of 20 years in eighteen, before the age of 10 years in seven, and in the remaining seven after the age of thirty. Only nine patients had any knowledge of a cardiac lesion before the age of thirty.

Fifty patients of the group reached the age of 50 years without subjective manifestations of heart disease. In four patients, more than eighteen years had elapsed between the initial discovery of a valvular lesion and the subsequent development of cardiac symptoms. In four cases, the first difficulty consisted of hemiplegia, vertigo, hemoptysis, and acute coronary thrombosis, respectively. The complication of subacute bacterial endocarditis occurred in only one instance. Chronic nontuberculous pulmonary disease, supposedly related to healed rheumatic pulmonary lesions, was frequently an associated finding and in twenty-nine of this number much of the respiratory distress could be blamed on pulmonary emphysema, chronic bronchitis, or pulmonary fibrosis. Chest roentgenograms were available in eighty-one of the patients, and in sixty-six instances there was definite x-ray evidence of pulmonary emphysema or abnormal bilateral

pulmonary fibrosis. The authors suggest that the cardiac failure may be due, in part, to the complicating pulmonary lesions which add another burden to an already strained right ventricle. Embolic phenomena, most often resulting in hemiplegia, occurred in eighteen patients, but auricular fibrillation was an associated finding in only ten cases of this number. Of the entire group of 106 cases, chronic auricular fibrillation existed in sixty patients. An abnormal cardiac silhouette was evident in most, but not all, of the eighty-one patients in whom roentgenograms of the chest had been made. In thirty-six instances the cardiac configuration was typical of mitral stenosis. In nineteen others, the enlargement was predominently that of the left ventricle, presumably due to a high degree of mitral insufficiency. In the entire series, the blood pressure of only thirty-two patients was found to exceed 150 systolic or 90 diastolic, and in only eighteen did the diastolic pressure exceed 100 millimeters. Among the thirty-two patients with hypertension, marked cardiac enlargement was present in twenty. A similar degree of enlargement was noted in only twenty-one of the seventy-five patients with a normal blood pressure. The electrocardiograms did not prove to be an important diagnostic aid, since right axis deviation occurred in only one-third of the cases. The findings in precordial leads are not mentioned.

Of the forty-four patients who were known to be dead at the time this report was prepared, the average age at death was 52.8 years, the oldest patient being 64 years of age. The most common cause of death was congestive heart failure, which varied in its duration from six months to ten years in different cases. Embolic episodes accounted for six deaths; subacute bacterial endocarditis, pneumonia, and malignancy were responsible for the remainder. The cause for the relatively benign course of the disease in the group of patients who formed the subject of this report remains a matter for speculation. The authors suggest that a mild initial rheumatic infection, unsucceeded by subsequent rheumatic episodes, permits a slow progressive valvular deformity to develop without much myocardial injury so that heart failure is delayed until the dynamics of the circulation are sufficiently disturbed by the valvular lesion.

WENDKOS

Rogers, H. M.: The Cardiovascular Manifestations of Induced Thyrotoxicosis; Report of Two Cases. Ann. Int. Med. **26:**914 (June), 1947.

Two cases are presented in whom auricular fibrillation developed after the ingestion of excessive amounts of desiccated thyroid substance. In both instances, discontinuance of the thyroid extract resulted in prompt resumption of normal sinus rhythm and disappearance of cardiac decompensation. The first case was that of a 63-year-old white woman who apparently had no organic heart disease and yet suffered from congestive failure induced by the thyrotoxicosis and auricular fibrillation. The second case was that of a 60-year-old white woman who also showed a bundle branch block in electrocardiograms made during the periods of auricular fibrillation and normal sinus rhythm, and yet did not develop congestive heart failure during the time she had auricular fibrillation.

WENDKOS.

Coller, F. A., Campbell, K. N., Berry, R. E. L., Sutler, M. R., Lyons, R. H., and Moe, G. K.: Tetra-ethyl-ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease, and Other Painful States. Ann. Surg. **125:**729 (June), 1947.

The authors investigated the therapeutic effects of tetra-ethyl-ammonium, a new compound, which has been found to block transmission of nerve impulses through autonomic ganglia. It was noted that parenteral injection of the drug in animals produced a fall in both systolic and diastolic blood pressure and an increase in peripheral blood flow, although it had no direct effect on arterioles. Furthermore, it did not prevent the derect peripheral action of epinephrine in raising blood pressure. In man, in addition, tetra-ethyl-ammonium produced dilatation of the pupil, loss of accommodation, cessation of sweating, dry mouth, and postural hypotension. No action of the drug could be demonstrated in a sympathectomized extremity.

Tetra-ethyl-ammonium was administered clinically, either intramuscularly or intravenously, in the form of a 10 per cent solution. The intravenous dose ranged from 100 mg. to a maximum of 500 milligrams. The authors utilized the drug in a series of patients suffering from causalgia

and related post-traumatic painful states and noted that in half of these, sustained relief of symptoms followed repeated injections. However, it was the opinion of the authors that autonomic blockades resulting from the use of the drug, which produced symptomatic relief in this group of patients, did not remove the indications for appropriate sympathectomy. Nevertheless, where the latter procedure was not feasible because of the presence of a marked psychogenic element or unstable personality, the use of tetra-ethyl-ammonium was indicated. In the case of herpes zoster and postherpetic neuralgia, some relief of pain, varying from a very brief period to six hours per block, was obtained in every instance, although more sustained improvement occurred in the patients with acute or subacute herpes zoster.

The authors found that in functional vascular disease, such as abnormal responsiveness to a cold environment, tetra-ethyl-ammonium was of diagnostic value, but it left much to be desired as a therapeutic measure. However, it was felt that in certain of the patients with Raynaud's phenomenon, attacks were aborted or modified in intensity

In the case of organic occlusive arterial disease, tetra-ethyl-ammonium was utilized as a therapeutic agent in that it relieved vasospasm, caused some relief of pain, and improved claudication. It was also of help in determining which patients might derive benefit from sympathectomy. Those with early to moderately advanced thromboangiitis obliterans experienced definite improvement either in the degree of pain or in the severity of claudication. However, in the case of the far advanced process with or without established gangrene, or in the presence of severe infection, the drug was of no avail. In the case of arteriosclerosis obliterans, it aided in the control of nocturnal pain but generally was of little value in improving claudication.

Tetra-ethyl-ammonium was utilized in individuals suffering from acute and chronic deep thrombophlebitis. An excellent response was noted in the instances of acute and subacute cases in the form of relief of pain and reduction of edema. The patients suffering from the sequelae of deep thrombophlebitis noted subsidence of edema and relief from pain and vasospasm. For the most part, the therapeutic effect was only temporary.

The authors advocated caution in the use of the drug in hypertensive patients, particularly in those in whom a neurogenic component existed. Precipitous falls in blood pressure on occasion occurred in these individuals, with temporary peripheral circulatory collapse. Elderly patients generally did not respond as well as did those in younger age groups.

ABRAMSON.

Friedland, C., and Sodi Pallares, D.: On the Significance of an M-Shaped Complex in the Precordial Leads V_1 and V_2. Arch. Inst. cardiol. México **27**:293 (June), 1947.

The authors studied eighty tracings with an M-shaped ventricular complex in Leads V_1 and V_2. In all of them, the duration of the intrinsic deflection was measured from the beginning of QRS to the vertex or the origin of the descending branch of R.[1] Roentgenograms of most cases and physical examination and necropsy of a few also were studied.

Nearly all tracings were recorded in patients with heart disease. Tracings with an M-complex in Leads V_1 and V_2 should be considered abnormal if other electrical abnormalities are present; otherwise, they should be considered as border line electrocardiograms. If the tracing is recognized as abnormal, there is a 72.5 per cent probability that it is connected with hypertrophy of the right ventricle, with or without simultaneous hypertrophy of the left. If the S wave has an amplitude of 4.5 mm. or more, hypertrophy of both ventricles is probable, though this conclusion requires the presence of other electrocardiographic abnormalities.

LUISADA.

Garcia Ramos, J., and Rosenblueth, S.: Studies on Flutter and Fibrillation III: The Self-Sustained Activity in the Isolated Auricular Muscle of Mammalians. Arch. Inst. cardiol. México **27**:302 (June), 1947.

A preparation of auricular myocardium with normal blood supply was obtained by crushing a narrow band around the base of the right auricular appendage in dogs and cats. The activity of the appendage then becomes independent from that of the rest of the auricle. Normal auricular tissue does not contract spontaneously. However, it may discharge impulses for several seconds

or minutes after injections of acetylcholine, adrenaline, or calcium chloride, and after application of stimuli at an appropriate rate. Different types of stimuli cause rapid automatic activity or slow automatic discharges over several seconds or minutes. The study deals mainly with the slow automatic activity.

The electrical phenomena of the isolated auricular appendage were recorded monophasically. Initiation of the propagated impulses usually was preceded by local negativity. However, Bozler's suggestion that spontaneous impulses are initiated by local potentials at the site of origin did not seem to be confirmed, as the impulses did not occur after a constantly fixed degree of local negativity.

Although the isolated auricular myocardium has no apparent automatism when separated from the sinoauricular node, it is potentially able to beat automatically, as shown by the fact that several stimuli are necessary to initiate the activity. The automatism of auricular myocardium resembles that of nodal tissues; it is accelerated by adrenaline, it is inhibited by acetylcholine and potassium ions, and may present a compensatory pause after a premature contraction.

A detailed study of the effects of adrenaline and acetylcholine is presented.

LUISADA.

Robles, C., and Benavides, P. H.: Considerations on Surgical Treatment of Essential Hypertension by Dorso-Lumbar Sympathectomy. Arch. Inst. cardiol. México **27**:408 (June), 1947.

The authors present some considerations on the possibilities of the Smithwick operation in hypertensive patients with advanced cardiac failure who do not respond to medical treatment. The history of five cases is reported. All patients reported were improved by the operation so far as heart failure was concerned; all showed a decrease in blood pressure. The response to medical treatment was good after surgery. The authors consider, therefore, that cardiac failure does not represent an absolute contraindication to sympathetic surgery. The conclusions are not absolute, however, because of the brief period of follow-up of the cases (one to two years).

LUISADA.

Marcuse, Peter M.: Nonspecific Myocarditis. Arch. Path. **43**:602 (June), 1947.

Marcuse collected thirty-six cases of myocarditis from a total of 3,800 autopsies, the diagnosis being made on microscopic examination of routine sections of heart muscle. Most of these cases showed extensive diffuse or focal myocarditis. Myocardial lesions of known etiology were excluded from this group, as were all cases serologically positive for syphilis. The majority were men less than 40 years of age.

The only gross change was cardiac hypertrophy, which was noted in fifteen cases (43 per cent); an occasional case showed grayish discoloration of the myocardium. The diagnostic microscopic changes were: (1) interstitial leucocytic infiltration, often perivascular; and (2) a secondary parenchymal destruction. Marcuse states that the only constant microscopic feature was the presence of elongated cells with large distorted nuclei, "different from the myocyte of Auitschkow and from Aschoff cells." They were not from degenerating muscle fibers, but probably were endothelial cells.

Practically all of these cases showed extracardiac inflammatory lesions, especially in the lungs. Bronchopneumonia and interstitial pneumonitis were the most commonly associated pulmonary lesions.

Clinical manifestations of cardiac involvement were vague; however, from a pathologic standpoint the incidence of "nonspecific myocarditis" is greater than generally assumed.

GOULEY.

Wilson, R. H., Mortarotti, T. G., and DeEds, F.: Some Pharmacological Properties of Rutin. J. Pharmacol. & Exper. Therap. **90**:120 (June), 1947.

Rutin, placed in the perfusion fluid surrounding excised segments of guinea-pig colon, was capable of prolonging the relaxation produced by epinephrine. The degree of prolongation was proportional to the dose of rutin. If given intraperitoneally in guinea pigs ten to thirty minutes prior to 50 per cent of the lethal dose of histamine, the mortality was reduced. Simultaneous administration of the two drugs showed no protection. In guinea pigs rendered scorbutic, the authors could demonstrate no significant difference in the animals' tendency to develop petechial hemorrhages in those given rutin and in those not given rutin. Therefore, the capillary permeability protective power of rutin could not be confirmed.

GODFREY.

Meyer, O.: The Ambulatory Treatment of Phlebitis, Thrombophlebitis and Thrombosis With Compression Bandages. Surgery **21**:843 (June), 1947.

The author advocates the use of compression bandages in the treatment of venous thrombosis and in the prevention of pulmonary embolism. He uses the combination of a medicated contura bandage applied loosely and a 3-inch-wide pressoplast bandage which is applied over it with strong nonconstricting pressure. The foot, leg, and thigh are covered but the knee as a rule remains free. The patient is then advised to walk as much as possible and to avoid standing.

According to the author, the application of the bandgages, using the optimal degree of pressure, will cause immediate relief of pain and rapid reduction in edema in the acute stage of deep thrombophlebitis. He presents statistical studies of others to support the view that with the use of compression bandages, pulmonary embolism is practically prevented. He also points out that the treatment must be supplemented by the removal of primary foci in the oral cavity and secondary foci in the jugular veins, to prevent reinfection of the veins of the leg.

ABRAMSON.

Hinchey, J. J., Hines, E. A., and Ghormely, R. K.: Osteoporosis Occurring During Potassium Thiocyanate Therapy for Hypertensive Disease. Proc. Staff Meet., Mayo Clin. **22**:275 (July 9), 1947.

The authors studied the records of 360 patients with hypertension to whom potassium thiocyanate had been given. Unexplained osteoporosis involving one or more extremities occurred in seven of these patients (2 per cent). A history of trauma or injury at onset was not present. Unexplained osteoporosis was not noted in the group of patients with hypertension who were not receiving potassium thiocyanate.

The average age of this group was 57 years. The dosage of the drug varied considerably during the course of treatment, but was usually in the range of 6 to 9 grains (0.4 to 0.6 Gm.) daily. The onset of symptoms associated with the osteoporosis generally occurred in from three to six months after the patient started taking the drug. They consisted of pain on use of the extremity and subsequent mild swelling of the joint or joints involved. Roentgenograms revealed mild to marked diffuse osteoporosis.

Active therapeutic measures directed toward the osteoporosis were carried out in seven cases while thiocyanate therapy was being continued. The symptoms continued to progress despite these measures in six cases. Slight improvement over a period of several months was noted in the seventh case and this was accelerated when the use of potassium thiocyanate was stopped. Cessation of treatment with potassium thiocyanate was followed by relief in every one of the seven cases whether or not specific measures of treatment of the osteoporosis were used. Use of the drug was resumed in four instances. In two neither the symptoms nor the osteoporosis recurred. Symptoms did recur in the other two and were again relieved when administration of thiocyanate was once more discontinued.

BELLET.

American Heart Association, Inc.

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Telephone Circle 5-8000

THE AMERICAN HEART ASSOCIATION PREPARES FOR INTENSIFIED EDUCATIONAL AND FUND-RAISING ACTIVITIES

Second National Heart Week, Feb. 8, 1948.—In the period that has elapsed since the first observance of National Heart Week last February, the American Heart Association has taken a major step forward in achieving public recognition and greater understanding of the heart diseases through its educational program. A continual stream of information has been released through the media of press and radio to publicize the three-point program of the Association: national research, public and professional education, and community service through the formation and activities of local heart associations.

The groundwork has been well laid for the development of a more comprehensive fund-raising and public relations program during the 1948 observance of National Heart Week, February 8-14. For the first time, a direct appeal will be made to the public for funds. As part of the fund-raising program, an integrated special gifts campaign will be conducted.

The full cooperation of national wire services, national magazines, and radio networks has been assured for the second annual Heart Week. Interest evidenced so far indicates that the observance will surpass the highly effective results achieved last year.

Following last year's procedure, Heart Week programs will be developed which can be coordinated with local heart associations, with the necessary community organization. In addition, it is planned to make a comprehensive drive among Community Chests to obtain their acceptance of the obligation of meeting a community quota for the attack against the heart diseases.

In order to bring the American Heart Association's educational campaign to many communities throughout the United States where there are no local heart associations, cooperation is expected again this year from the United States Junior Chamber of Commerce, the American Legion, Rotary International, and Kiwanis International.

The business and professional women's clubs of New York State will conduct fund-raising activities for the American Heart Association with the support of their sixty community organizations.

To assist these groups with their educational and fund-raising programs the American Heart Association will make available a plastic heart-shaped collection box created by the eminent designer, Stanley Chamberlain; a publicity kit consisting of suggested news releases, editorials, and radio scripts; educational pamphlets and leaflets; a series of three posters dramatizing the story of heart disease and rheumatic fever; a film on heart disease as it affects the average businessman and his family; and a film strip on rheumatic fever.

The nation's leading chain drugstores have agreed to display the plastic heart on counters throughout the United States. It will be mounted on a counter card bearing the legend, "Open Your Heart . . . Give to Fight the Heart Diseases, America's Number One Killer."

Independent druggists and other groups are also cooperating in utilizing the plastic heart.

Creation of Local Heart Associations.—Of equal importance with the fund-raising program is the campaign for the creation of additional local heart associations throughout the United States. In the last analysis, the financial stability of the American Heart Association will depend on the structure and number of local affiliates.

In response to numerous requests received by the American Heart Association for assistance in the formation of local heart associations and in the development of local programs, "A Guide to the Formation of Local Affiliates of the American Heart Association" was recently published. The aim of this booklet is to suggest basic procedures and indicate solutions to many of the problems which arise in the formation of affiliated associations.

In an introduction to the Guide, Dr. A. R. Barnes, president of the Association, points out that vital research in diseases of the heart and circulation has lagged far behind minimum requirements because of lack of community support. "Community cardiovascular programs have only recently begun to emerge," Dr. Barnes says, "and these have been too few in number to meet the overall needs of the public."

Emphasizing further the need and place of the local heart associations, Dr. Barnes says:

"The American Heart Association provides a comprehensive program to deal with the broad aspects of diseases of the heart and blood vessels. The ultimate success of this program depends on an effective organization of local heart associations.

"The local heart association is the task force in this struggle. This has been demonstrated adequately in those areas where strong local heart associations already exist. There is need for similar strong organizations in every important community. These must be active and show initiative in meeting problems peculiar to their individual areas.

"As to the national agency, the American Heart Association is organized to guide and integrate the functions of the local associations, and to serve as a clearing house for their activities. But it is the local heart associations which must do the field work. Through their efforts it will be possible to bring the benefits of scientific research in cardiovascular disease to every citizen in every community in the United States."

ANNUAL MEETING

The Annual Meeting and Twenty-first Scientific Session of the American Heart Association will be held in Chicago, Illinois, on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings and for the Annual Dinner which will take place on Saturday evening, June 19.

The Chairman of the Program Committee for the Annual Scientic Session is Dr. Herrman L. Blumgart, 330 Brookline Avenue, Boston, Massachusetts. All who desire to present papers at the meetings in Chicago on June 18 and 19 should forward to Dr. Blumgart an abstract of the proposed presentation of not more than 500 words. The dead line for the receipt of abstracts is Feb. 1, 1948.

INDEX TO VOLUME 33

AUTHORS INDEX

An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

C

D

E

F

G

H

S

T

U

V

W

Y

Z

SUBJECT INDEX

An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

B

C

D

M

N

T

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Review of Books.—Publishers and authors are informed that the space of the Journal is so fully occupied by matter pertaining to the branches to which it is devoted that only works treating of these subjects can be noticed. Deserving books and monographs on physiology, pathology, and diseases of the heart, circulation, blood, and blood vessels will be reviewed when space is available. Send books to the Editor-in-Chief, Dr. Thomas M. McMillan, Clinton Street Bldg., Pennsylvania Hospital, 330 S. 9th Street, Philadelphia 7, Pa.

BUSINESS COMMUNICATIONS

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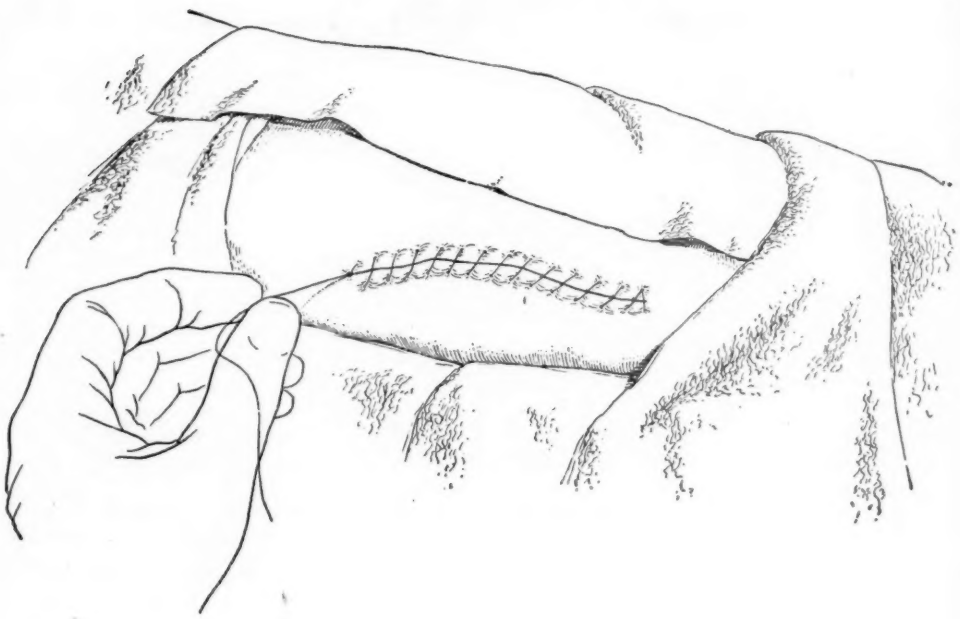

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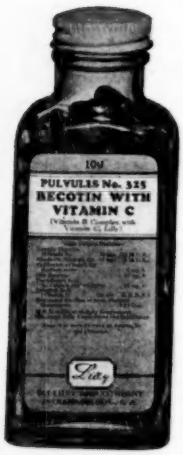

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